Seminars in Cancer Biology xxx (xxxx) xxx

Contents lists available at ScienceDirect

Seminars in Cancer Biology

journal homepage: www.elsevier.com/locate/semcancer

Review

# Paradoxes of cancer: Survival at the brink

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ARTICLE INFO

*Keywords:*
Cancer atavism
Reversible polyploidy
Self-organisation
Cancer "life-cycle"
Aneuploidy
Bivalency

ABSTRACT

The fundamental understanding of how Cancer initiates, persists and then progresses is evolving. High-resolution technologies, including single-cell mutation and gene expression measurements, are now attainable, providing an ever-increasing insight into the molecular details. However, this higher resolution has shown that somatic mutation theory itself cannot explain the extraordinary resistance of cancer to extinction. There is a need for a more Systems-based framework of understanding cancer complexity, which in particular explains the regulation of gene expression during cell-fate decisions. Cancer displays a series of paradoxes. Here we attempt to approach them from the view-point of adaptive exploration of gene regulatory networks at the edge of order and chaos, where cell-fate is changed by oscillations between alternative regulators of cellular senescence and reprogramming operating through self-organisation. On this background, the role of polyploidy in accessing the phylogenetically pre-programmed "oncofetal attractor" state, related to unicellularity, and the de-selection of unsuitable variants at the brink of cell survival is highlighted. The concepts of the embryological and atavistic theory of cancer, cancer cell "life-cycle", and cancer aneuploidy paradox are dissected under this lense. Finally, we challenge researchers to consider that cancer "defects" are mostly the adaptation tools of survival programs that have arisen during evolution and are intrinsic of cancer. Recognition of these features should help in the development of more successful anti-cancer treatments.

## 1. Definitions of paradox and two cognitive approaches to cancer

Science often progresses through the recognition of paradoxes and the collision of opposing theories. Cancer displays a series of paradoxes. The Oxford Dictionary defines paradox as "a seemingly absurd or contradictory statement or proposition, which when investigated may prove to be well-founded or true". A cited example is the uncertainty principle in physics which "leads to all sorts of paradoxes, such as particles being in two places at once". This example of something being in two places at once will be explored throughout this review as a concept of how cell fate decisions are resolved, particularly in Cancer. 'Being in two places at once' in complex biological systems translates into the ability to elicit rapid transitions from one state to another. These transitions can happen at both single cell and population levels and in both cases involves a general reordering of the system at hand "at the brink". This rewiring happens through 'Self Organization'. Self-organization is a process by which a system becomes re-arranged and frequently leads to new properties i.e. a sort of 'domino effect' that leads to an alternative (but permitted in energetic terms) configuration of the system, triggered by an external stimulus. This alternating shift, back and forth, implies the simultaneous presence of the two alternative configurations, i.e what we defined as 'being in two places at once'. The same happens when different cells in the same tissue can be in different states regarding the population cell fate [1]. Our current inability to routinely cure metastatic cancer hints at our lack of understanding of its complexity [2]. Self-organization of living systems, which are regulated far from equilibrium within their environment, is a key to their complexity [3], displayed also in the genome organisation [4] and likely is a key to the paradoxes of cancer. It is only through further study and understanding that we can resolve contradictory observations, therefore it is important to first recognise and define the underpinning characteristics of Cancer, and then define the paradoxes before seeking to resolve them.

There are two essentially linked features of cancer cells - immortality and resistance to extinction (treatment resistance) – characteristics to which all cancers evolve [5,6]. Concerning the latter, when observing the survival response of various tumours to ionizing radiation and genotoxic drugs, a common response is precipitous early cell death in

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https://doi.org/10.1016/j.semcancer.2020.12.009
Received 2 November 2020; Received in revised form 7 December 2020; Accepted 9 December 2020
Available online 16 December 2020
1044-579X/

the first week after treatment, followed by almost inevitable tumour recovery and cancer relapse – a capacity which does not obey a linear relationship and can be characterised as "survival at the brink". This capacity underpins the ability of the system to undergo a low probability event to escape from adverse conditions by self-organisation as described above, through a rapid transition to another, more favourable, state. In the following text, adopting the terminology commonly used in Physics, we will refer to such stable states as 'attractors'. An attractor means that a given configuration of a system is sufficiently stable such that when the effects of an eventual perturbation disappear it comes back to the original state [3] - (see also below in Paragraph 2)

There are two broadly opposing concepts of cancer. The first takes the position that as cancer represents pathology, something is "wrong and broken" in these cells: they are stochastically mutant and epigenetically dysregulated and the progression of cancer is associated with accumulation of this disorder. A plethora of aberrant cancer genotypes, karyotypes, and phenotypes (intratumoral heterogeneity) supports this assertion [7,8]. Here, Cancer cell survival and progression is thought to occur through a combination of random mutations and the Darwinian selection of the fittest clones within an individual's tumour [9–11]. However, this still most popular somatic mutation theory (SMT) has a central caveat; because mutations are random, often neutral [12] and rarely positive, the accumulation of lethal mutations – Muller's ratchet [13] should inevitably occur. The second view proposes that stress/oncogene-induced senescent cancer cells instead use trial and error for rescue by explorative adaptation and rewiring by self-organisation of their gene regulatory network (GRN) - the "genome orchestra". The same intratumoral heterogeneity as mentioned above also supports this theory. The GRN, setting a functional genome at the state of the equilibrium of its constituents within the environment, is "the pre-programmed attractor' - one of its possible pre-programmed stable configurations (a "sink" towards which a genome tends to evolve at the given conditions) [14]. As predicted by S. Kauffman [15–17] and supported by recent cancer gene expression phylostratigraphy results (described in Paragraph 4), "Cancer attractor" is pre-programmed within the early phylo-ontogenetic evolution of life. It can be accessed by reprogramming under times of genomic stress allowing survival, whilst de-selecting unfavourable phenotypes. Such regulation by self-organization through creative disorder seems to be the only way to ensure the survival of minor cell populations at the brink of death under threat of extinction [18]. The two concepts of cancer outlined above characterised by the same presence of aberrant, heterogenic karyotypes and phenotypes also represent a cognitive paradox, needing comprehension and reconciliation. To better define this second approach, below we introduce a key method of regulation by self-organization - creating order out of chaos.

## 2. Order out of chaos

The concept of "survival at the brink" is in fact a sublimated metaphor for the regulation of living systems through the laws of (non-equilibrium) thermodynamics. A system complexity was described as life at the edge of chaos, between order and disorder" [3], involving fluctuations, and reciprocal causation [1,18,19]. Prigogine who obtained a Nobel Prize in 1977, and Prigogine with Stengers [20], designated this kind of regulation as "order out of chaos", proposing this as "Man's new dialogue with nature". Here, the biological systems are described as dissipative. A *dissipative system* is a thermodynamically open *system* which is operating out of, and often far from, thermodynamic equilibrium, in the environment with which it exchanges energy and matter [21]. Prigogine and Stengers [20] stated that "at a certain threshold of the control factor, the system loses stability (reaches a bifurcation point), behind which it begins to coherently fluctuate its parts (Fig. 1A)". The choice between two different stable states (symmetry break) then becomes a stochastic event, however, its probability may depend on the presence of a positive feedback loop (Fig. 1B), e.g.

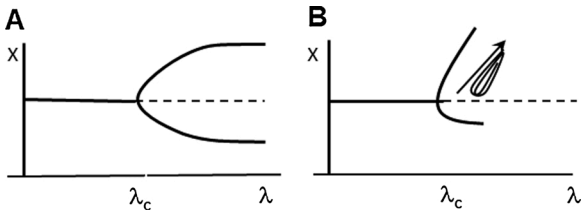


**Fig. 1.** Principles of the thermodynamic regulation of dissipative systems. (A) Scheme from Prigogine and Stengers [20] showing symmetric bifurcation of the system: the change of the parameter X is a function of the bifurcation (control) parameter λ. When $\lambda < \lambda c$ the system is in only one stable state. At $\lambda > \lambda c$ (where λc is a certain threshold of the control λ parameter (e.g. the amount of DNA strand breaks) the system becomes unstable, starts to fluctuate and can stochastically occupy each of two stationary states (e.g. DNA repair or apoptosis). (B) Indicates the impact of a self-organising attractor, shown here as a positive feedback loop (e.g. local concentration of growth factors), which collectively increases the probability of the system going in one particular way of the two possible.

local high concentration of a growth factor released by a neighbour cell.

Importantly, this kind of regulation is not directly based on random genetic mutations (which are rare and too slowly clonally selected) and is used by cells and populations to adapt to "unforeseen challenge" [22], during catastrophic threats [23,24]. The same method of chaotic self-organisation is also used during pre-programmed cell fate changes in early embryogenesis, wound healing, differentiation and transdifferentiation [1,25–31]. Explorative adaptation, involving the search of potential cell states, presumes epigenetic genome plasticity and heterogeneity requiring multi-potent stemness [32] and operates by fluctuating between alternative cell fate options - being "in two places at once" in the interim, respectively, canalizing instructively suitable and permissively possible pathways and sorting/de-selecting unsuitable phenotypes [33,34]. Explorative adaptation through chaotic regulation explains why genomic instability and stemness are intrinsic to cancer - they are its instruments of resistance to extinction (discussed in more detail below).

In non-equilibrium transition states, the "statistical outliers" may be the forerunners of the ongoing change [16,35], while the heterogeneous distributions of the opposite components (e.g. intratumoral heterogeneity) witness chaotic and oscillatory regulations [8,20,36] – with the cells "being in two places at once". The cellular senescence which should prevent malignancy is often seen not only preceding it but paradoxically even favouring resistance to cancer treatments [37–39].

The latest data show that accelerated cellular senescence induced by cancer drugs represents, in fact, an exploration mechanism for cell fate change by "survival at the brink" and an excellent example of the cell "being in two places at once".

## 3. Cellular oscillators and the paradox of cellular senescence cooperating with stemness

To facilitate "order out of chaos", cells have various oscillators, whose activity is based on positive and negative feedback loops, starting from the circadian clock to ultradian rhythms regulating the cell cycle and ending in metabolic oscillators [40]. The single most important tumour suppressor and guardian of the genome P53 [41] also works through this mechanism. P53 and its regulator Mdm2 represent an oscillatory pair (Fig. 2A,B), with P53 driving Mdm2 transcription, which in turn serves to ubiquitinate P53, reducing its presence. This dynamic feedback loop has been nicely demonstrated by Lahav and colleagues using fluorescent reporters of the two proteins in irradiated MCF7 cells [42,43]; moreover, they and others also showed that these cells do not recover from DNA damage if the oscillations in P53 expression are replaced by sustained activation [44,45]. Here, in the presence of DNA damage and sustained expression of P53, the explorative adaptation

required for finding/rewiring a GRN for survival attractor becomes impossible; the maintenance of P53 effectively equivalent to cell death. Indeed, the stable reintroduction of wt P53 into P53 mutant cancer cells kills them [46].

In a series of experiments with the ovarian wt *tp53* embryonal carcinoma cell line PA1, treatment with the topoisomerase II inhibitor, Etoposide, introduced DNA double-strand breaks (DSB) in S-phase, alongside signs of cellular senescence (Sa-b-gal positivity, persisting DSBs, CHK2 signalling, and up-regulation of P53) we also observed [47] the dual and heterogeneous up-regulation of two opposing regulators of senescence/apoptosis in the same cell – P21 (Cip1) and the key stemness factor Pou5f1 (Oct4) (Fig. 2C, D). Further examination revealed that the expression of both regulators was induced by the same trigger – upregulated P53 in response to DNA damage; however, the activity of P21 was reciprocally moderated by Oct4 as schematized in (Fig. 2E) thus limiting cell death and providing greater time for DNA repair.

Moreover, this induced Oct4A underwent transcriptional splicing (by methylation of *pou5f1/oct4* gene enhancers) produce the transactivation-inactive isoform Oct4B (Fig. 2F) before re-asserting its usual transcriptional activities in surviving cells. 2–3 weeks after treatment, when DNA damage and P53 were reduced in the surviving cells, this feed-back loop ceased [48,49]. Thus an alternation between OCT4A and OCT4B forms by alternative splicing leading to the alternating of the damage repair and self-renewal was found. This series of experiments reveal the unique capability of the tumour suppressor P53 to facilitate not only genome fidelity but also the preservation of self-renewal potential in embryonal stem (carcinoma) cells [50]. The protective capacity of P53 was also found by Halliday et al. [51]. In turn, Kalmar et al. [52] using fluorescent reporters, directly described an Oct4-Nanog oscillator of pluripotency in embryonic stem cells (Fig. 2G). Another putative senescence-stemness oscillator, P16ink4a-Nanog, was encountered in triple-negative breast cancer cells resistant to neoadjuvant therapy (Fig. 2H-J) [53]. This behaviour can be explained by similar oscillatory mechanisms also in mutant TP53 cells selecting an "escape" from (the reversal of) senescence between opposite options of GRN state spaces. Similar antagonism was revealed by [54], and dual P16ink4a-Nanog expression was observed in an irradiated epithelial liver stem cell line [55].

In comprehending these oscillation junctions, one can understand the paradox of accelerated cellular senescence induced by oncogenic-, oxidative- or genotoxic-stress, whereby senescing cancer cells access reprogramming to achieve multi-potent stemness [38] in the search for the survival attractor, thereby recover to become more resistant than before experiencing senescence [38,53,56,57]. However, as shown in BRAF-mutant melanoma, these cells can be epigenetically reversed back to senescence [58]. Thus, the accelerated cellular senescence paradoxically favouring cell self-renewal and survival can be explained by reaching the bifurcation point with the critical number of DSBs initiating oscillation between opposite regulatory pathways as indicated in Fig. 1A, with two options, each of them randomly attainable in an individual cell. It can be speculated that a chain of coherent molecular oscillators, such as those highlighted in Fig. 2, facilitate a "green light" (in physics, termed "limit cycles" [40]) channelling DNA damaged senescing cells through the permissive GRN states (in space and time) that finally allow rare cells to successfully reach a salvage attractor (according to the scenario depicted in Fig. 1B). In fact, the same mechanism of channelling through a prolonged series of senescence-associated meta-states is observed during somatic reprogramming. For example following the "Yamanaka cocktail" (Oct4, Sox2, Klf4 and c-Myc) <1% of mouse embryonic fibroblasts become reprogrammed to the "ground state'' of a GRN capable of delivering pluripotency [14], but also of producing transformation [59]. In turn, the

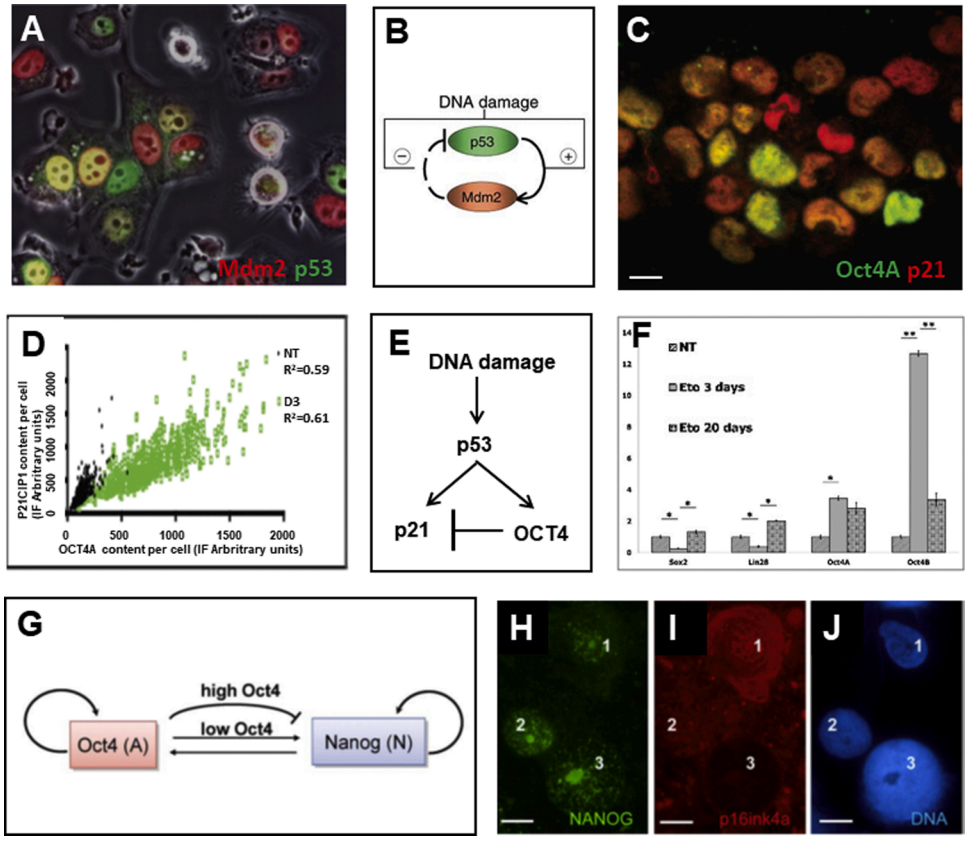


**Fig. 2.** Evidence of cancer and embryonic stem cells displaying opposing regulators of cell fate defining self-renewal, senescence or death. (A, B) The p53-Mdm2 oscillator detected in irradiated MCF7 breast cancer cells by live-cell imaging of coloured reporters p53 (green); Mdm2 (red) and (B) a scheme of the oscillator (reproduced from [42,43]) License Number 4, 944,291,233,368 (Springer Nature); (C-F) Embryonal carcinoma PA1 cells after treatment with Etoposide: (C,D) dual and heterogeneous immunofluorescent pattern of the opposing regulators Oct4 (green) and p21/CIP1 (red) expressed in the same cells, at the stage (day 3-5 after treatment), before clonogenic recovery (reproduced from [47]); (E) schematic of the DNA damage-p53 induced regulators p21 and OCT4, with OCT4 moderating p21 expression, as shown by mechanistic experiments [48]; (F) temporary overexpression of the POU5-F1/OCT4A splicing form OCT4B (lacking the 1st exon and transactivating capacity) with down-regulation of the LIN28 and SOX2 members of the stemness transactivation network in etoposide-treated PA1 cells on day 3, compared to recovered clones (day 20) [49]; (G) The Oct4A-Nanog oscillator revealed in embryonic stem cells (reproduced from [52] CC BY 3.0); (H-J) Three neighbour cells from a primary triple-negative breast cancer sample resistant to neoadjuvant therapy stained for NANOG and p16INK4A, self-renewal and senescence regulators, showing three patterns – dominating p16, approximately similar expression, and exclusively NANOG expression in a polyploid cell nucleus. Bars = 10 μm [53]).

paracrine acting senescence-associated secretome consisting of growth factors, cytokines, and extracellular proteases modulating the micro-environment [60] can be considered as an additive and important permissive resource for the collective channelling of the 'dominant path" towards the recovery of senescent cells [34,61]. However, if these survival resources (including recycling of nutrients by autophagy) are exhausted, terminal senescence takes over channelling the death-path through overproduction of P21/Cip1 and P16ink4a proteins leading to cell nucleus disintegration [48,62]

As discussed above, accelerated cell senescence represents an instrument of preprogrammed cell fate change, challenged by oncogenic, genotoxic or oxidative stress, which can bring forth the cancer attractor and resistance to death. As predicted by S. Kauffman [15–17], the "Cancer attractor" is pre-programmed within the early phylo-ontogenetic evolution of life. This leads us to consider the evolutionary history of cancer and its exploration through gene expression phylostratigraphy as described in the next paragraph. Here another paradox - the somatic mutation theory of cancer (SMT) and atavistic theory of cancer are in contradiction [63] and need further comprehension. The central problem of this conundrum, in our view, is how cancer cells achieve immortality and their mode of reproduction.

## 4. The source of cancer cell immortality and the atavistic shift of cancer cells towards unicellular organism gene expression networks

Somatic cells are mortal – they undergo the Hayflick limit of telomere shortening with each cell cycle [64] and subsequently senesce and die. However, somatic cancer cells are immortal, replicating and dividing *in vitro* after the death of their host and growing at transfer in syngeneic animals endlessly. Although tissue stem cells can replenish the dead cells, this reserve is also limited and our body dies. The immortality of cancer cells can be explained by our hypothesis [65] of the replacement of the limited replicative capacity of somatic mitotic reproduction with the unlimited reproductive relay of sequential life-cycles, transmitting immortality 'between generations", akin in life-cycles of unicellular organisms which are essentially immortal. Indeed, the phenotypic similarity of giant cancer cells with unicellulars was noted in our early work [66]. The theory of heredity through the transmission of the germ-line between life-cycles of generations was first proposed by August Weismann [67] and provides a pillar of fundamental biology. As the evolutionary life-cycles are various and phylogenetically programmed [68], it is, therefore, appropriate to consider the phylogenetic history of cancer.

Which evolutionarily conserved programs might the mutant and non-mutant but also stressed ("senescent") cells use, with the potential

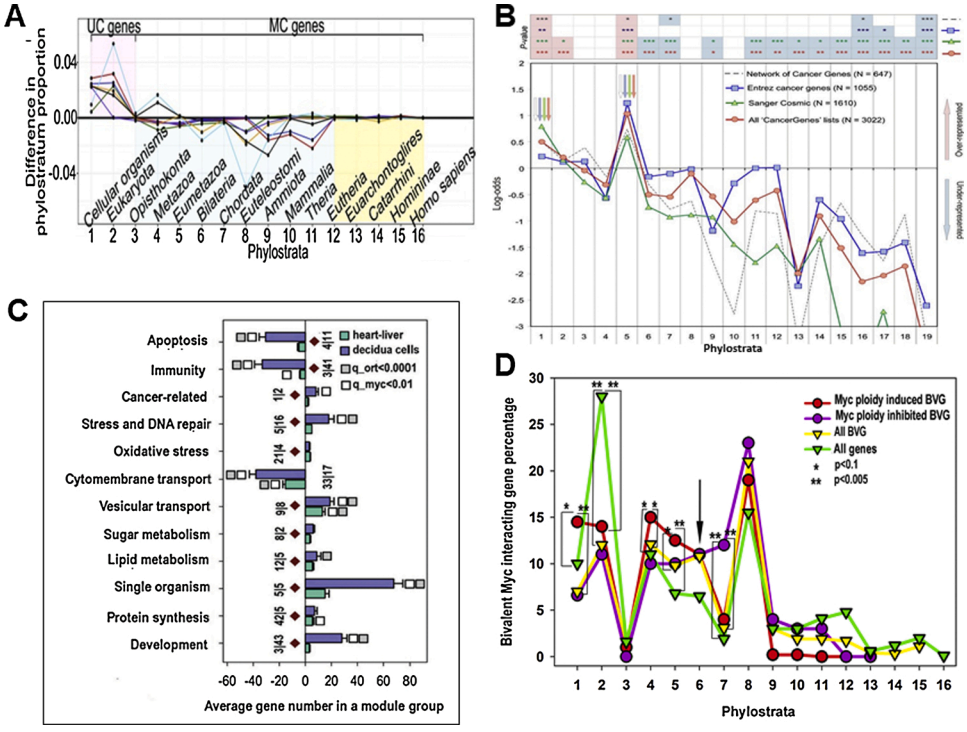


**Fig. 3.** Phylostratigraphic and modular distribution of gene expression through evolution and through polyploidy: (A) Genes that date back to unicellular (UC) ancestors are preferentially over-expressed in seven types of tumours versus normal tissues (reproduced from [72] Copyright (2017) National Academy of Sciences); (B) Phylostratigraphic representation of log-odds statistics of human cancer gene expression levels, based on four different datasets (see inset on top right). Arrows designate the strongest significant over-representations. (* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$). Significant over-representation and under-representation are shaded in red and blue, respectively (reproduced from [71] CC BY 3.0); (C) Common ploidy associated changes in gene function module groups for heart, liver and 4n/2n decidua cells revealed by PCA for *myc* interacting genes. Gene modules for a single organism, development, stress and DNA repair are upregulated, while modules of apoptosis, immunity and membrane transport are down-regulated. White and grey squares reflect q values for module functional group enrichment significance with regard to all *myc* targets (white squares) and with regard to all genes in the genome (grey squares). Module groups confirmed by transcriptome pair-wise comparison are marked with brown diamonds (reproduced from [115] CC BY 3.0); (D) The effect of the polyploidy-associated *c-myc* targetome on phylostratigraphic distribution of genes with bivalent chromatin shows enrichment of mostly activated bivalent genes that date back to unicellular and early multicellular ancestors and the opposite enrichment of ploidy inhibited bivalent genes after the cross-point at stratum 6 (arrow). Gene expression difference is >2-fold. * $p < 0.05$, ** $p < 0.01$. *c-myc* polyploidy targetome was taken from [115], 1st Supplement, the list of bivalent genes from [120], phylostratigraphic classification, the same as used by [72], from http://www.ncbi.nlm.nih.gov/taxonomy.

to lead to immortality linked to cancer? The human genome is composed of two interconnected gene nexuses, derived from the unicellular and multicellular [69,70]. Gene expression phylostratigraphic analysis shows that cancer is most closely aligned with the atavistic genetic programs of development elaborated by unicellular organisms at their transition to multicellularity [69,71–75] manifested by a change in the gene expression balance in relation to evolutionary age, in favour of the oldest genes, while suppressing genes originated more recently, in complex multicellular organisms (Fig. 3 A, B). Here, it is important to further highlight that this epigenetic shift to unicellular gene expression profiles is aided by whole genome duplications (WGD; as shown in paragraphs 5–8, below) and is associated with a particular mode of reproduction of cancer cells. Usually, cancer researchers consider only the mitotic cell cycle. However, in the last two decades, >20 independent groups have shown that cancer cells can also reproduce through reversible polyploidy (ploidy cycles) and that the polyploid giant cancer cells (PGCC) are important in metastases and resistance to genotoxic treatments [26,76–80]. This fact still remains poorly recognized by the wider cancer research community.

## 5. Polyploid giant cancer cells, whole-genome duplications, and ploidy cycles

PGCCs are the diagnostic and prognostic hallmarks of aggressive cancer [80,81]. Polyploidy, whole-genome duplications (WGDs) are well known in evolution as a source of diversification of gene homologs and thus the creation of new species [82–85]. Generative (i.e. whole organism) WGD appears in particular in unfavourable habitats and provides, besides gene diversification by random mutations, the resource for adaptation of species through three means: 1) multiple genomes mask deleterious mutations and can decrease their impact by recombination [68]; 2) polyploid cells can facilitate rapid adaptation in adverse conditions, in particular also by higher protein synthesis, tolerance of hypoxia and toxicity and more [83,84,86]; 3) ploidy cycles (orderly doubling and halving of genomes) are associated with the evolution of sexual reproduction [87]. Ploidy cycles emerged initially to elicit DNA strand breaks repair and to relieve, by recombination, the mutational load of aneuploidy resulting from occasional polyploidy [88–90]. Ploidy cycles as such should counteract, or moderate, aneuploidy. Ploidy cycles within asexual unicellular organisms gave rise to the origin to meiosis (developed from endomitotic to zygotic, and finally gametic meiosis) and sexual reproduction for maintaining reproductive fidelity, genetic diversity, and species identity [91–93]. WGD in *Arabidopsis* induces a clear set of eight meiotic genes involved in chromosome juxtaposition and chiasma formation [94]. Polyploidy is a spandrel of asexuality with the transition to sex [95]. In sexual organisms, polyploidy usually occurs in adverse conditions by non-reduction of gametes leading to a parthenogenetic life-cycle [84]. So, the evolutionary ploidy cycle has a relationship to asexual life cycles, the origin of meiosis and sex, as well as adaptive facultative sex, parasexual cycles, and unisexual parthenogenesis. In all cases, it is dealing with whole genomes and complementarity. A ploidy cycle is a synonym (or part) of a life-cycle and the material base of heredity transfer between generations [68]. Transient cyclic polyploidy emerged in some life-cycles of still extant unicellular organisms, particularly Radiolaria [92] is more cost-effective than permanent diploidy or permanent polyploidy [68,88]. Although generative WGD appears in all evolutionary classes, starting from prokaryotes [96], most metazoan species tend to return to generative diploidy after adaptation to new habitats, albeit sometimes after many generations, often through a “triploid bridge” [68,82,97–100] and associated, at least, in some tumour types, with resistance to genotoxic drugs [53,81]. The necessity to return to diploidy is due to the intrinsic chromosome instability of the polyploid genome [101] which often results in aberrant segregation of chromosomes during mitotic divisions by break-bridge-fusion cycles [102], multipolar mitosis [103], chromosomal and structural aberrations; the generative polyploidy also presents difficulties in ordered segregation during canonic meiosis, for faithful reproduction of species. As such, organisms use the advantages of WGD in evolution, accepting (and possibly, moderating and counteracting) the disadvantage of the resulting genome instability and aneuploidy [68,82,83,104,105]. The adaptivity of WGD is also used for somatic polyploidy – in normal mammalian organogenesis and to accommodate an increased functional load in some organs, e.g. the heart and liver [106,107]. Therefore, to estimate the impact of polyploidy *per se* and to allow comparison with cancer data, we investigated the phylostratigraphic effect of somatic polyploidy in normal mammalian cells. The same shift to unicellularity was revealed.

## 6. Polyploidy and the shift to unicellularity in normal mammalian tissues

Somatic polyploidy is rare in mammalian organs, with some exceptions [108,109] and the DNA amount in these polyploid cells, except those involved in regeneration or senescence, is relatively oligo-polyploid with relatively low levels of aneuploidy [9,108,110–112] and own observations).

Applying bioinformatic analysis of gene expression data for three simultaneous pair-wise cross-species transcriptome comparisons of polyploid versus diploid mammalian tissues (human and mouse heart, liver, decidua), we observed a shift towards unicellularity of Gene Ontology and Biosystem modules. The most important are the modules of single-cell organism metabolism (GO:0044710), catabolism (GO:0044712), biosynthesis (GO:0044802), membrane organisation (GO:0044711) and reproduction (GO:0044702) [113–115] *C-myc*--driven epigenetic reprogramming is well known as favouring the onset of tumorigenesis by inducing a stem cell-like state [59,116]. *myc* normally regulates the cell cycle but if overexpressed, uncouples DNA replication from cell division and induces polyploidy [112,115,117]. Thus, c-myc overexpression (often amplified and usually not-mutated) is coupling polyploidy with the cancer-initiating stemness. The *c-myc* targetome upregulated by polyploidy and examined using the principal component analysis (PCA) revealed a unicellular organism module, development, cancer-related, stress and DNA repair pathways, while suppressing immunity, apoptosis, and transmembrane transport (Fig. 3C) [115]. The link between polyploidy and ancient unicellular features mediated by *c-myc* was also found [113–115]. In addition, the full transcriptome analysis also revealed the phylostratigraphic shift from multicellularity to unicellularity [114]. Moreover, we disclosed the role of genes with bivalent chromatin, often the targets of *c-myc*-induced transcriptional pause release [118] involved in the polyploidy-dependent shift in gene expression towards unicellularity, overcoming intervening species barriers as shown below.

## 7. Genes with bivalent chromatin in polyploidy, meiosis, and cancer: being in two places at once

Genes with bivalent chromatin (also termed “bivalent genes”) are those, whose enhancers and/or promoters contain chromatin regions of suppressing H3 lysine 27 methylation harbouring smaller regions of activating H3 lysine 4 methylation. These domains tend to coincide with genes of transposable elements expressed at low levels. These genes were identified as the regulators of cell fate change in embryonic stem cells [119,120]. As such, this bi-valency mechanism is again based on the uncertainty principle, acting when there is a choice between two options - gene expression is either paused (poised) by suppressive H3K27me3 histone modulation or rapidly activated by H3K4me3 modifications. However, bivalent H3K27me3 and H3K4me2/3 domains are not limited to developmental promoters, but also underlie reversible silencing of somatic/progenitor genes during the mitosis-to-meiosis transition in spermatogenesis; as well as being involved in the reverse process after fertilisation [121]. In other words, these bivalent genes can potentially facilitate cell fate change through both multi-potency and

the transition from mitosis to meiosis to initiate a ploidy life-cycle and facilitate its return to the mitotic cycle. Interestingly, using the gene expression dataset for normal cell polyploidy [115], we revealed a highly significant ($p < 10^{-16}$) enrichment of bivalent genes in the ploidy-associated full transcriptome and the *c-myc* interactome, as well [114]. The phylostratigraphic distribution of the latter is presented in Fig. 3D. It coincides in general with the changes in phylostratigraphic landscapes in cancer versus normal tissues and cancer genes as presented in Fig. 3A and B and supports the epigenetic control of cancer by bivalent chromatin regions reported earlier [122]. "Poised" chromatin allows rapid switching on/off of key developmental genes through the thermodynamics of bivalent chromatin self-organisation. Conflicting chromatin states, like bivalency, are associated with high transcriptional noise promoting system explorative fluctuations for cell fate change [35,123]. Also, the moderate activation of transposable elements coinciding with bivalent regions should increase the amplitude of these coherent fluctuations. This self-organising mechanism should allow low probability events, such as cell-fate change, to occur [1,124]. The protein-protein String network, Gene ontology module and Kegg cancer pathway analysis using data from bivalent gene expression patterns plus the c-myc targetome related to polyploidy, revealed upregulation of ABC drug resistance (of Prokaryotic origin), embryonic development, and cancer pathways in early multicellulars, while the pathways of multicellular complexity - cell communication, differentiation, immunity and apoptosis were all downregulated [114], thus indicating a tendency towards the dissolution of tissue organization. Subsequently, we arrived at the conclusion that the cancer atavistic shift to "unicellularity-based-multicellular-state" ensuring drug resistance and onco-fetality, is highly enhanced by polyploidy. The phylostratigraphic data [69,71–73] witness in favour of the atavistic theory of cancer beyond species [73,125–127] and suggests that cancer programs are salvaged from the unicellular and early multicellular forms of life. However, we still need to better reconcile these proposals with the oldest, embryological, and then the chromosomal theory of cancer.

## 8. Is the Embryological or Atavistic theory of cancer correct? – both

There is a long history of the inter-relationships between cancer and embryogenesis dating from the 19th century [128–133]. It has been shown by nuclear transplantation that cancer cell nuclei can prime embryogenesis [134,135], while embryonal cells can develop into tumours if ectopically placed into adults; multiple experiments brought Barry Pierce to the conclusion that there must be an embryonic field capable of regulating every kind of carcinoma [133,136]. The similarity between embryo and cancer can be also found in the paradoxical features of reversible cellular senescence [137,138] and genome instability [139–141] displayed by both. Moreover, similar observations and the capacity of PGCCs to differentiate into three germ layers [142] and to produce a metastasising tumour from only one PGCC transplanted into a mouse [143] are at the basis of the current twist of the embryological theory of cancer connecting it with polyploidy. Furthermore, the phenotypes seen in the early cleavage embryo are (parthenogenetically?) recapitulated in aggressive tumours containing the early-embryo-like polyploid giant cancer cells (PGCC), which are transiently dominating in proportion after genotoxic treatments of TP53 mutant tumours [26,78,79,132,133,142,144,145]. How are these embryonal features related to cancer atavism?

The "cancer attractor" was previously suggested as an evolutionary relic space-state of GRN with a near-zygotic developmental potential, unused but accessible, in the mammalian genome [15,17,146]. The bivalent epigenetic control of oncofetal genes in cancer cells has been also shown previously [147]. A careful comparison of the gene phylostratigraphic profiles obtained by three independent groups and presented in Fig. 3 A,B, and D and also for whole transcriptomes by [114] provides a supporting argument. Namely, in Fig. 3A, the phylostratigraphic data presented by [72] for seven tumour types versus normal tissues, reveal, along with upregulation of the first two unicellular strata, an increase at early multicellularity stratum 4 gene expression (Metazoa) for two of seven tumour types, however stratum 5 (Eumetazoa) in this dataset is ambivalent, while the 6th stratum - Bilateralia and further – are under-expressed. However, Domazet-Lošo et al. [71], using four different cancer-related gene expression datasets unequivocally indicate, in addition to the first two unicellular strata, a significant oncogenic upregulation in stratum 5 (Fig. 3B). As if summarizing both observations, our phylostratigraphic analysis presented in Fig. 3D demonstrate that the upregulation of bivalent genes by *c-myc* and polyploidy includes strata 1, 2 (unicellulars), stratum 4 (metazoa) and prominently, by upregulation stratum 5, while a point of the bi-stable switch between upregulated and suppressed bivalency falls upon stratum 6 with sharply opposing suppressive epigenetic effect starting from the next stratum 7 (Vertebrates). Summarizing these findings, it appears that carcinogenesis emerged in cooperation of the unicellular genes with the genes of the Metazoa and Eumetazoa strata, favoured by *c-myc* driven reprogramming (*c-myc* provides a pivotal link between malignancy and stemness [59,115,148] and its induced WGD. These processes are assisted by genes with bivalent chromatin, allowing crucial cell fate change by self-organisation, which may include the mitotic-meiotic transition [121] and the development of the parthenogenetic embryo [68,88] - an analogue of a PGCC [130–133]. It should be highlighted that in this same Eumetazoan stratum 5 of the evolutionary life-tree the basic processes of early embryonic development (including gastrula stage) emerged and remained conserved in mammals [149].

## 9. The reciprocal mitotic-ploidy "cancer life-cycle"

Somatic polyploidisation is usually initiated after genotoxic insult by the re-union of two mitotic daughter cells with regression of the cleavage furrow or even fusion after its full abscission resulting in a bi-nuclear cell [150]. Theoretically, this is a primitive act of syngamy (automixis) [68,92], similar to that seen in normal mammalian organs [108], and observed in irradiated HeLa cells. Multinuclear cells may also be formed from binuclear ones through asymmetric divisions and multipolar a-cytokinetic mitosis [151,152]. Nevertheless, in many cancers, the process of polyploidisation is started from aborted metaphase - "mitotic slippage" [153] - caused by persistent telomere damage (senescence), bypass of mitosis and transition to tetraploidy [154,155]. It is likely that the tetraploid cells induced by genotoxic insult and acquiring embryonal stemness [93,156,157] allowing cell fate change enter a particular 4n phase preventing the destruction of cyclin B1 and thus preventing anaphase [158] by the meiotic kinase Mos. In this way, cell fate change can be evoked – by shifting from the canonical mitotic cell cycle into the meiosis-initiated parasexual ploidy cycle.

For example, in a doxorubicin-treated breast basal cancer cell line, the cells re-replicate by mitotic slippage daily and stepwise to reach 8C, then 16C and 32C DNA content (Fig. 4A, B). From this "developmental totipotency checkpoint" (analogy of morula stage), reached by many tumours in various models (and also described in some insect organs) [159,160] a stepwise return to 2C for reciprocal production of mitotic descendants is started (Fig. 4C, D) [76,157,161]. Correspondingly, the ordered reduction divisions (two examples are shown in Suppl. Fig. 1A, B), including binemic bi-polar segregations, cell divisions omitting S-phase and other meiosis-like elements [151,162–164] can be observed, albeit aberrant and chaotic metaphases are also encountered (Suppl. Fig. 1C). A reciprocal relationship between a step-wise genome doubling and then halving is also shown in Fig. 4E and F. These observations, first described by Illidge et al. 2000 [76] and [161] demonstrate, strictly saying, an asexual ploidy cycle [68,88], termed also for Radiolarians "cyclic polyploidy" [92]. Besides *c-myc* activation, the genotoxically induced polyploidisation is accompanied in TP53 mutants by up-regulation of key stemness transcription factors – Oct4, Sox2, Nanog [165], Wnt-Notch signalling [166], DNA repair of DSBs by

homologous recombination [167]; Ki-67-positivity, and DNA synthesis inferred by the inclusion of BrdU [76,157]. These stemness features are combined in polyploidizing cells with the hallmarks of accelerated senescence, such as Sa-b-gal-positivity and telomeric DNA damage [154, 155,168] - the paradoxical composition of opposites in accelerated cell senescence explained above in Part 3. The DNA damage during mitotic slippage is sorted out for autophagy in micronuclei [55,62,169]. We found recently that cytoplasmic DNA resulting from mitotic slippage is selectively enriched with telomere ends [157,170] and see Suppl. Fig. 1D-F [157]. In addition to Mos-kinase, 'Mitotic slippage" is also accompanied by upregulation of the genes and proteins of meiotic ovogenic prophase - SPO11, DMC1, RAD51, REC8, OCT4A, VASA, FRAGILIS (Fig. 4G) and [157] supporting the mitotic-meiotic transition as a component of the ploidy cycle (defined in Part 5). Ovogenic, embryonal, placental, and testis- associated genes were found in experiments on several tumour cell lines and over a very wide range of human patient cancers correlating with poor prognosis [93,152,156, 164,170–175]. Such a massive presence of germ genes in 33 somatic and germ tumour types as directly tested by [176] cannot be a purely stochastic effect of genomic instability imposed onto mitotic cycle by ectopically expressed meiotic genes as supposed by some researchers [175,177–179]. It is certainly part of the programmed parasexual" cancer life-cycle" [65,77,113,156] composed of the reciprocally joined mitotic (somatic) and ploidy (germline) circuits (Fig. 5). Interestingly, in some cancers, the repeated mitotic slippage cycles can bring to atavistic phenotypic amoeboid conversion.

## 10. Amoeboid conversion, budding of offspring

Not only embryo-like phenotypes [80,132,133,180] but also amoeba-like phenotypes have been encountered in observations of DNA-damaged PGCCs. The amoeboid giant cells appear in the second-week post-DNA- genotoxic treatments. The cells develop a powerful cytoskeleton, exhibit cannibalism [181], migration [182], encystment and excystment [113,159] (Suppl. Fig. 2A). Through mitotic slippage, they demonstrate the epigenetic drift from epithelial to mesenchymal (amoeboid) transcriptional and phenotypic identity [157]. This transition is also characterised by the release of the cellularized subnuclei, resembling sporogenesis of Protozoa, e.g resulting from cycling polyploidy in asexual *Entamoeba histolytica* and *invadens* [183,184] and *Amoeba* species; in the latter (*Amoeba vulgaris*), after considerable chromatin diminution [185–187]. Such observations of 'budding' offspring from PGCC were reported by several authors in different cancer models [66,142,145,157,159,188,189]. Rajaraman [190] documented this cyclic process by video cinematography and highlighted it as a parasexual somatic reduction division in cancer (and termed it "neosis" [188]).

It should be also noted here that asymmetric reduction division of maturing oocytes, wherein polar bodies are released during anaphase through an actin ring [191,192] is similar to sporogenesis and the asymmetric reduction divisions observed in some PGCC, suggesting their mutual nature – examples from four DNA-damage stressed tumour types are presented in Suppl. Fig. 2. In the case of parthenogenesis, a polar body is further reunited with the female pronucleus and is also very similar to the processes observed in the amoeboid. The budding

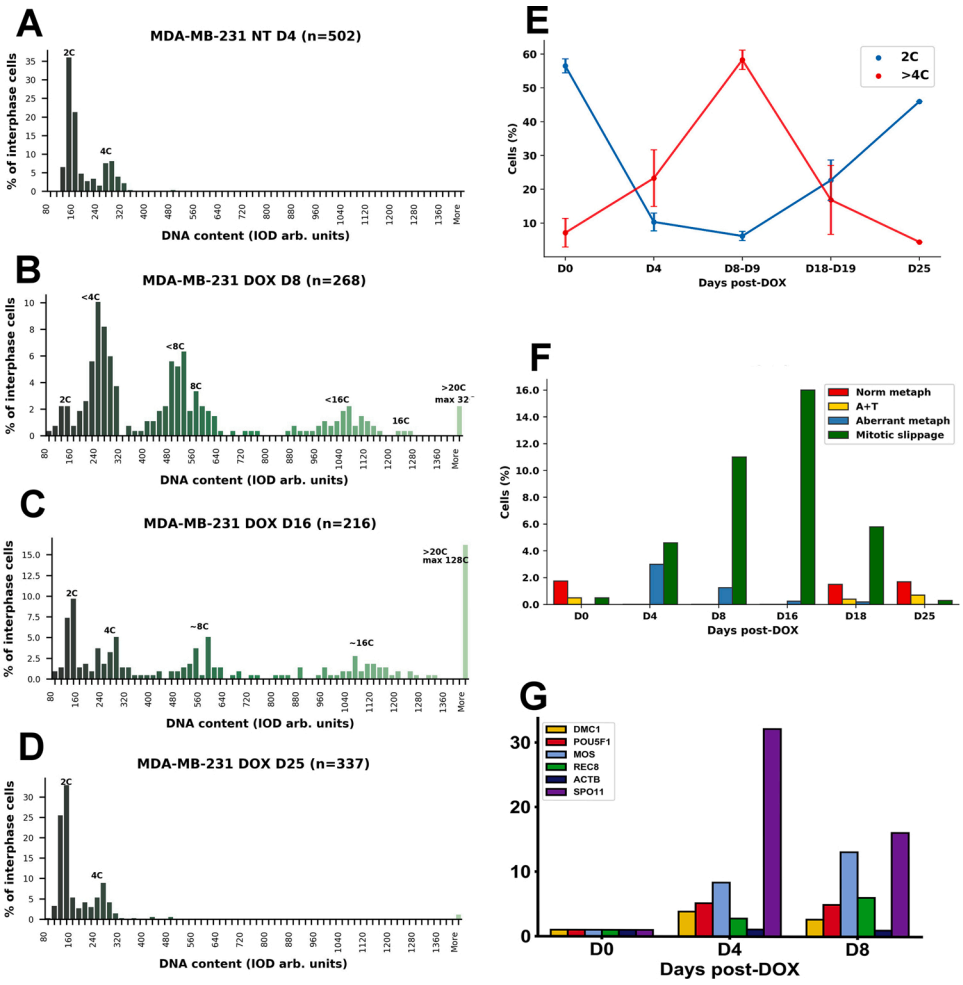


**Fig. 4.** Ploidy response of MDA MB 231 cells after treatment with doxorubicin (DOX; 100 nM, 24 h) over 25 days. (A-D) Histograms of DNA content obtained by in situ DNA cytometry of individual interphase cell nuclei showing stepwise polyploidisation by day 8 post-treatment and a stepwise depolyploidisation by day 16. The bifurcation of depolyploidising and continuing polyploidisation sublines, clearly seen, on day 16, precedes the recovery of the normal cell cycle with practical disappearance of hyperploid cells on day 25; (E) Reciprocal relationship between 2C and polyploid (>4C) cells in the time course after DOX treatment in three independent experiments; (F) DNA in situ staining and microscopy analysis to assess mitosis in the same DOX-treated MDA MB 231 cells. The data shows aberrant metaphases and increasing 'mitotic slippage" along with polyploidisation cycles, with the return to the normal mitotic cycle with anatelophases, on day 18 and full recovery, on day 25; (G) RT-PCR results for stemness and meiotic genes in post-DOX MDA MB 231 cells, enhanced with the emergence of the polyploidising "mitotic slippage" cycles. The representative chart of two independent experiments, with three technical replicates. Reproduced from [157].

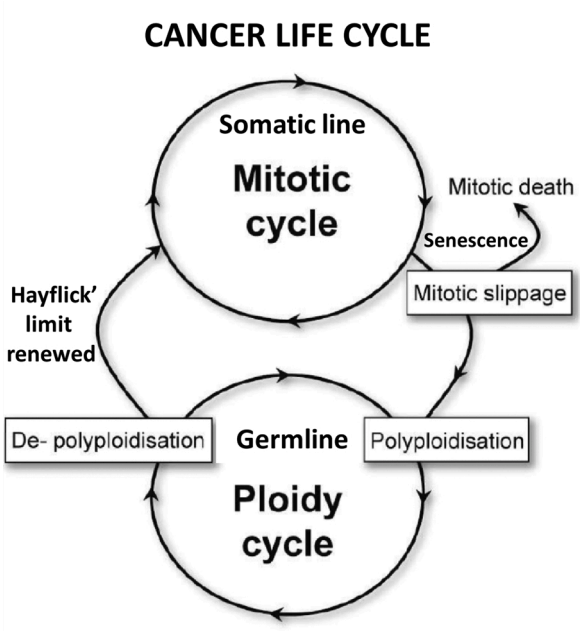


**Fig. 5.** Schematic of cancer "life-cycle" reciprocally uniting a mitotic cell cycle of the somatic line and a ploidy cycle of the germline, with mitotic slippage from senescence on one side and renewal of the Hayflick' limit through telomere renewal on the other. The ploidy cycle is associated with a transient dual senescence/stemness state, activation of meiotic genes and replacement of telomere ends. We hypothesize that the ploidy cycle is present at a low basal level in untreated cancer cells supporting the maintenance of genomic fidelity and immortality, being much enhanced after genomic damage/stress, providing cancer treatment resistance. Modified from [65,113,156].

from a PGCC in mitotic anaphase is also occasionally encountered in non-treated cancer cells (Suppl. Fig. 2C) or in the minority of polyploids, even seven weeks after clonogenicity was restored from polyploidy in drug-resistant clones (Suppl. Fig. 2E) hinting to a basic cyclicity of this process hidden in cancer. In addition, cellularization of the bi-polarly dividing syncytial blastoderm nuclei in Drosophila multinuclear embryo (which underwent "superficial cleavage cycles" before that) segregating germ and somatic cells [193] may also be a noteworthy evolutionary analogy of the processes observed in PGCC recovering offspring from DNA damage [133].

In summary, both modes of PGCC asexual reproduction (embryonic/parthenogenetic and sporogenic-like) belong to variants of the same cancer ploidy cycle schematised in Fig. 5. Our analysis thus strengthens the phylogenetic origin of ontogenesis-like processes in tumours discussed in Part 8 and by [194].

## 11. "Supergiant" nurse-cells and catastrophic mitosis

In addition, DNA cytometry of the doxorubicin-treated breast cancer cell line has revealed that at the critical point of depolyploidisation of the reproductive PGCCs, another cell population becomes branched – achieving much more extensive polyploidy and increasing in proportion (Fig. 4C). This fraction is transient and practically disappears after the recovery of the resistant cell line (Fig. 4D). These amoeboid "supergiants", which very likely derive from the same precursor as the reproductive subline, and which can elicit very high aneuploid DNA content (up to ~ 400C) "obstinately" enter catastrophic mitosis, displaying chaotically arranged and fragmented chromosomes (Suppl. Fig. 1C), and either undergo apoptosis or restitute interphase again. Similar "obstinate supergiants" were also observed in long-term cultures of irradiated HeLa cells (personal observations). These "supergiants" with apparently chaotic genomes appear to serve as nurse-cells – providing molecular substrates (e.g. soluble DNA), mechanical support and possibly a vehicle for the recently "born" small mitotically-capable 'offspring" - see Suppl. Fig. 3 [157]. This situation is somewhat similar to the cooperation of the egg with nurse-cells produced by a single germline stem cell in the Drosophila ovary germarium [195], which polytenize and further undergo programmed cell death [196]. Prieur-Carrillo [197] following the fate of the irradiated PGCC of bladder carcinoma cells by video-cinematography, also noted that part of giant cells underwent stepwise reduction divisions, while another part did not. These observations are also compatible with the reproductive subline of PGCC undergoing encystment and sporogenesis and a somatic subline, which can interconvert in stress conditions in *Entamoeba histolytica* and *invadens* [183]; Niculescu found in this behaviour an analogy with atavistic cancer stem cells. Similar is the evolutionary strategy of creating functionally different polyploid subpopulations in mammalian trophoblasts adjusting to the animal lifestyle [198]. Cancer amoeboids display an example used by Nature of the essential cooperation of two daughter cell types, of the same origin, for survival at the brink or beforehand of extinction. Besides these extraordinary examples of ameboid conversion in human breast cancer cells, we also observed islands of cartilage differentiation with normal-sized cell nuclei and also neuronal-type nestin-positive cells. These phenotypes did not persist, being outcompeted through re-seeding by surviving clearly malignant clones. Similar observations were reported previously by several authors (reviewed by [36]), alongside the concept of cancer "life-code" from pathologist observations [144,199] substantiating the origin of benign and malignant (PGCC-including) tumours from the upper and root parts of the ontogenetic tree, correspondingly. In summary, we conclude that there are many evolutionary links between mammalian embryogenesis, protozoan sporogenesis, insect gametogenesis and embryogenesis, and reproduction of PGCCs. These observations and evolutionary analogies provide a viable biological explanation for the immortality of cancer cells through similar parasexual life cycles as exemplified in Fig. 5.

Again, this is another example of the reciprocal causation providing a cell "being in two places at once", that residing either in the rapid and short mitotic cycle (~20 h) or slow and prolong ploidy cycle (~2–3 weeks) unnoticed by researchers performing shorter, 3–5-day long experiments [78]. The capability of cancer cells to extend the Hayflick limit by maintaining proliferation through reinitiating telomerase activity is part of this parasexual mechanism. Importantly, during senescence-associated cancer "life cycle" ("neosis"), the Hayflick limit was proposed to be reset each time anew [129,190]. Indeed, during mitotic slippage, the telomere replacement and recombining through transient alternative telomere lengthening after removing the damaged telomere ends, and then re-establishing new TERT-positive telomeres in mitotic offspring was revealed in the DOX-treated MDA MB 231 cells [157]. Noteworthy, a similar replacement of telomere ends has been reported in Ascaris cleavage embryo during the switch from the germ-to-somatic cell line [200], in the classic model of the chromatin diminution [201].

## 12. The Cancer aneuploidy paradox - between genomic order and chaos

Interestingly, the aneuploidy and chromosome theory of cancer described by Hansemann and Bovery was conceived in the same period when gametogenic (embryonic) ideas of tumour formation were circulating [128,130,202]. Aneuploidy alters and even hinders cell division but paradoxically is a hallmark of cancer, increasing with tumour progression, grade and resistance to therapy [10,203–205]. In general terms, an explanation for this paradox was provided in the 2nd section of this review – that in dissipative systems, the order is created by explorative adaptation "out of chaos" [20].

This means that initiation and evolution of cancer towards the evolutionary pre-programmed "cancer attractor" described above is achieved through trial and error, thus, is accompanied by a plethora of intermediate, unsuccessful, aberrant karyotypes, variable epigenomes

[8] and non-clonogenic karyotypes [206], which also serve adaptive exploration and in this sense, indirectly, clonogenic survival. It is becoming clear that aneuploidy and chromosome instability is an excellent source of the genomic chaos needed for cell fate change by reprogramming [10,11,207]. Rapid 'punctuated' karyotype rearrangement in one mitotic cycle, "chromothripsis", found in ~50 % of cancers, is associated with polyploidy, telomere attrition and DNA damage sorting by micronucleation [208–210]. It may arise during polyploidisation through "mitotic slippage" [211] serving initiation of the PGCC ploidy cycle on the one hand, and ultimate restoration of the mitotic progeny, on the other [105,157] as already discussed. However, full genome breakage may occur in the supergiant "nurse-cells", which likely have a mutual precursor with the reproductive stemline and which "obstinately' enter catastrophic mitoses, fragment chromosomes (to prepare the substrate DNA for their nurselings?), and although having a limited life-span and being ultimately non-reproductive, seem vital for tumour progression. Hyper-production of reactive oxygen species by the hyper-metabolic cancer giants may favour this catastrophic mitotic explosion [212,213].

At the same time, aneuploidy can be directly used for adaptive evolution in stress environments both in unicellular organisms [214] and cancer [215]. Interestingly, the negative pre-selection of clones with loss of heterozygosity and even gene conversion proposed previously for asexual polyploid unicellular species by Maciver [216,217] as a route of escape from Muller's ratchet, was recently found in human cancer [218]. The parasexual character of the giant cell ploidy cycle is consistent with several observations, whose analysis is out of scopes of this review. We can only briefly mention here the evolutionary conserved maternal and paternal genomic autonomous behaviour (gonomery) [163] exposed in stressed normal cells, while similar uniparental genome separation was found in a proportion of the embryonal carcinoma and basal breast cancer, along with signs of non-canonical inverted meiosis [105,157]. We also found the pedogamic exchange in tripolar mitosis with a haploid genome between diploid and triploid sub-populations of cancer cells [99], which is also an interesting parasexual feature explaining "the ordering of the aneupolyploid genomes". All these observations need further studies and implementation into the cytogenetics of cancer. Not the least, the longitudinal transcriptional and genetic analysis of single cells of clonal colon cancer populations reveal that genetic sub-clonal structure in cancer cells can be diversified and progressed non-genetically, by epigenetic memory [219].

## 13. Conclusion

From the reviewed data, one can see that the creation and complex division events that occur with PGCC have evolutionary and adaptive analogues in nature. These "aberrations" are far more than simply random events driving cancer through the principles of Darwinian clonal selection. Rather, there is a growing understanding of the adaptive character of cancer genome chaos. Currently, considering the thermodynamics of cancer, with priority given to epigenetically preprogrammed chaotic regulations, both embryonal and chromosomal (aneuploidy) theories appear principally correct. However, the relationship of aneuploidy and genome instability with programmatic parasexual ploidy cycles seen in cancer, particularly in their resistance to DNA damage, only briefly reviewed here show that we still have a long way to go to incorporate them fully in the context of the atavistic embryological features of cancer. As described earlier, always in science – to fully comprehend, we must first observe the paradoxes, establish the principal facts and then delve deeper to resolve them. The coming years will hopefully provide the solution to the key paradoxes of cancer that facilitate its final extinction.

## Declaration of Competing Interest

The authors declare that there are no conflicts of interest.

## Acknowledgement

Alexander Vinogradov and Alessandro Giuliani are acknowledged for help and advice in gene phylostratigraphic studies, Harry Scherthan, in FISH experiments and to Pawel Zayakin and Ninel M Vainshelbaum for reading the manuscript.

*Funding*

This work was supported by a grant from the European Regional Development Fund (ERDF) projects No. 1.1.1.2/VIAA/3/19/463 for K.S. and partly from No. 1.1.1.1/18/A/099 for J.E.

## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.semcancer.2020.12.009.

## References

[1] M. Mojtahedi, A. Skupin, J. Zhou, I.G. Castaño, R.Y.Y. Leong-Quong, H. Chang, A. Giuliani, S. Huang, Cell fate-decision as high-dimensional critical state transition, Syst. Biol. (Stevenage) (2016) 287.
[2] R.A. Weinberg, Coming full circle-from endless complexity to simplicity and back again, Cell. 157 (2014) 267–271.
[3] R. Lewin, Complexity: life at the edge of chaos, Collier Books (1993).
[4] T. Misteli, Self-organization in the genome, Proc. Natl. Acad. Sci. U. S. A. 106 (2009) 6885–6886.
[5] V. Walther, C.T. Hiley, D. Shibata, C. Swanton, P.E. Turner, C.C. Maley, Can oncology recapitulate paleontology? Lessons from species extinctions, Nat. Rev. Clin. Oncol. 12 (2015) 273–285.
[6] K.J. Pienta, E.U. Hammarlund, R. Axelrod, S.R. Amend, J.S. Brown, Convergent evolution, evolving evolvability, and the origins of lethal cancer, Mol. Cancer Res. 18 (2020) 801–810.
[7] L. Sansregret, C. Swanton, The role of aneuploidy in Cancer evolution, Cold Spring Harb. Perspect. Med. 7 (2017), https://doi.org/10.1101/cshperspect.a028373.
[8] R.R. Beach, C. Ricci-Tam, C.M. Brennan, C.A. Moomau, P.-H. Hsu, B. Hua, R. E. Silberman, M. Springer, A. Amon, Aneuploidy causes non-genetic individuality, Cell. 169 (2017), 229–242.e21.
[9] S.J. Pfau, A. Amon, Chromosomal instability and aneuploidy in cancer: from yeast to man, EMBO Rep. 13 (2012) 515–527.
[10] M. Giam, G. Rancati, Aneuploidy and chromosomal instability in cancer: a jackpot to chaos, Cell Div. 10 (2015) 3.
[11] C.J. Ye, Z. Sharpe, H.H. Heng, Origins and consequences of chromosomal instability: from cellular adaptation to genome chaos-mediated system survival, Genes 11 (2020), https://doi.org/10.3390/genes11101162.
[12] M.J. Williams, B. Werner, C.P. Barnes, T.A. Graham, A. Sottoriva, Identification of neutral tumor evolution across cancer types, Nat. Genet. 48 (2016) 238–244.
[13] H.J. Muller, The relation of recombination to mutational advance, Mutat. Res./Fundam. Mol. Mech. Mutag. 1 (1964) 2–9.
[14] S. Huang, Reprogramming cell fates: reconciling rarity with robustness, Bioessays. 31 (2009) 546–560.
[15] S. Kauffman, Differentiation of malignant to benign cells, J. Theor. Biol. 31 (1971) 429–451, https://doi.org/10.1016/0022-5193(71)90020-8.
[16] S. Huang, G. Eichler, Y. Bar-Yam, D.E. Ingber, Cell fates as high-dimensional attractor states of a complex gene regulatory network, Phys. Rev. Lett. 94 (2005), 128701.
[17] S. Huang, I. Ernberg, S. Kauffman, Cancer attractors: a systems view of tumors from a gene network dynamics and developmental perspective, Semin. Cell Dev. Biol. 20 (2009) 869–876.
[18] J. Erenpreisa, A. Giuliani, Resolution of complex issues in genome regulation and Cancer Requires non-linear and network-based thermodynamics, Int. J. Mol. Sci. 21 (2019), https://doi.org/10.3390/ijms21010240.
[19] E. Karsenti, Self-organization in cell biology: a brief history, Nat. Rev. Mol. Cell Biol. 9 (2008) 255–262.
[20] I. Prigogine, I. Stengers, Order out of Chaos: man's new dialogue with nature, Flamingo (1985).
[21] V. Parmon, Thermodynamics of Systems That Are Far From Equilibrium, Thermodynamics of Non-equilibrium Processes for Chemists With a Particular Application to Catalysis, 2010, pp. 113–171, https://doi.org/10.1016/b978-0-444-53028-8.00003-4.
[22] E. Braun, The unforeseen challenge: from genotype-to-phenotype in cell populations, Rep. Prog. Phys. 78 (2015), 036602.
[23] J. Erenpreisa, A. Budylin, Related changes in RNA synthesis and DNA superhelicity during starvation of Ehrlich ascites tumour cells, Proc. Latv. Acad. Sci, Ser B. 10 (1990) 90–94.

[24] A. Budylin, J.E. Erenpreisa, A. Zhukotsky, N. Zaleskaya, Fluctuations of the reparable DNA strand breaks in starving tumour cells, Proc.Latv.Acad.Sci. B. 5 (1993) 72–73.
[25] H.I. Roach, J. Erenpreisa, T. Aigner, Osteogenic differentiation of hypertrophic chondrocytes involves asymmetric cell divisions and apoptosis, J. Cell Biol. 131 (1995) 483–494.
[26] S. Moein, R. Adibi, L. da Silva Meirelles, N.B. Nardi, Y. Gheisari, Cancer regeneration: polyploid cells are the key drivers of tumor progression, Biochim. Biophys. Acta Rev. Cancer 1874 (2020), 188408.
[27] J. Erenpreisa, Tamed'chaos in embryonal development and carcinogenesis: a holistic view, PRoceedings-Latvian Academy of Sciences Section B (2000) 1–8.
[28] J. Erenpreisa, H.I. Roach, Epigenetic selection as a possible component of transdifferentiation, Further study of the commitment of hypertrophic chondrocytes to become osteocytes, Mechanisms of Ageing and Development. 87 (1996) 165–182, https://doi.org/10.1016/0047-6374(96)01703-4.
[29] M. Zernicka-Goetz, S. Huang, Stochasticity versus determinism in development: a false dichotomy? Nat. Rev. Genet. 11 (2010) 743–744, https://doi.org/10.1038/nrg2886.
[30] M. Tsuchiya, V. Piras, M. Tomita, K. Selvarajoo, Collective fluctuations are crucial for global biological response, in: Nature Proceedings (2010) 72–75.
[31] M. Tsuchiya, A. Giuliani, K. Yoshikawa, Cell-fate determination from embryo to Cancer development: genomic mechanism elucidated, Int. J. Mol. Sci. 21 (2020), https://doi.org/10.3390/ijms21134581.
[32] S. Huang, Systems biology of stem cells: three useful perspectives to help overcome the paradigm of linear pathways, Philos. Trans. R. Soc. Lond., B, Biol. Sci. 366 (2011) 2247–2259.
[33] J.A. Weston, Principles of development and differentiation C. H. Waddington, BioScience. 16 (1966) 821–822, https://doi.org/10.2307/1293653.
[34] M. Bizzarri, A. Giuliani, M. Minini, N. Monti, A. Cucina, Constraints shape cell function and morphology by canalizing the developmental path along the Waddington's landscape, BioEssays. 42 (2020) 1900108, https://doi.org/10.1002/bies.201900108.
[35] H.H. Chang, M. Hemberg, M. Barahona, D.E. Ingber, S. Huang, Transcriptome-wide noise controls lineage choice in mammalian progenitor cells, Nature 453 (2008) 544–547.
[36] A.O. Pisco, S. Huang, Non-genetic cancer cell plasticity and therapy-induced stemness in tumour relapse: "What does not kill me strengthens me,", Br. J. Cancer 112 (2015) 1725–1732.
[37] M. Serrano, A lower bar for senescence, Nature 464 (2010) 363–364, https://doi.org/10.1038/464363a.
[38] M. Milanovic, D.N.Y. Fan, D. Belenki, J.H.M. Däbritz, Z. Zhao, Y. Yu, J.R. Dörr, L. Dimitrova, D. Lenze, I.A. Monteiro Barbosa, M.A. Mendoza-Parra, T. Kanashova, M. Metzner, K. Pardon, M. Reimann, A. Trumpp, B. Dörken, J. Zuber, H. Gronemeyer, M. Hummel, G. Dittmar, S. Lee, C.A. Schmitt, Senescence-associated reprogramming promotes cancer stemness, Nature 553 (2018) 96–100.
[39] E. Sikora, J. Czarnecka-Herok, A. Bojko, P. Sunderland, Therapy-induced polyploidization and senescence; coincidence or interconnection? Semin. Cancer Biol. (2020) https://doi.org/10.1016/j.semcancer.2020.11.015.
[40] D. Gilbert, D. Lloyd, The living cell: a complex autodynamic multi-oscillator system? Cell Biol. Int. 24 (2000) 569–580.
[41] M.B. Kastan, Wild-type p53: tumors can't stand it, Cell. 128 (2007) 837–840.
[42] G. Lahav, The strength of indecisiveness: oscillatory behavior for better cell fate determination, Sci. STKE 2004 (2004) e55.
[43] G. Lahav, Oscillations by the p53-Mdm2 feedback loop, Adv. Exp. Med. Biol. 641 (2008) 28–38.
[44] J.E. Purvis, K.W. Karhohs, C. Mock, E. Batchelor, A. Loewer, G. Lahav, p53 dynamics control cell fate, Science 336 (2012) 1440–1444.
[45] M. Choi, J. Shi, S.H. Jung, X. Chen, K.-H. Cho, Attractor landscape analysis reveals feedback loops in the p53 network that control the cellular response to DNA damage, Sci. Signal. 5 (2012) ra83.
[46] D. Lang, S.J. Miknyoczki, L. Huang, B.A. Ruggeri, Stable reintroduction of wild-type P53 (MTmp53ts) causes the induction of apoptosis and neuroendocrine-like differentiation in human ductal pancreatic carcinoma cells, Oncogene 16 (1998) 1593–1602, https://doi.org/10.1038/sj.onc.1201665.
[47] T.R. Jackson, K. Salmina, A. Huna, I. Inashkina, E. Jankevics, U. Riekstina, Z. Kalnina, A. Ivanov, P.A. Townsend, M.S. Cragg, J. Erenpreisa, DNA damage causes TP53-dependent coupling of self-renewal and senescence pathways in embryonal carcinoma cells, Cell Cycle 12 (2013) 430–441.
[48] A. Huna, K. Salmina, J. Erenpreisa, A. Vazquez-Martin, J. Krigerts, I. Inashkina, B. I. Gerashchenko, P.A. Townsend, M.S. Cragg, T.R. Jackson, Role of stress-activated OCT4A in the cell fate decisions of embryonal carcinoma cells treated with etoposide, Cell Cycle 14 (2015) 2969–2984.
[49] M. Baryshev, I. Inashkina, K. Salmina, A. Huna, T.R. Jackson, J. Erenpreisa, DNA methylation of the Oct4A enhancers in embryonal carcinoma cells after etoposide treatment is associated with alternative splicing and altered pluripotency in reversibly senescent cells, Cell Cycle 17 (2018) 362–366.
[50] J. Erenpreisa, K. Salmina, M.S. Cragg, Accelerated Senescence of Cancer Stem Cells: A Failure to Thrive or a Route to Survival? Senescence - Physiology or Pathology. (2017) https://doi.org/10.5772/intechopen.68582.
[51] J. Halliday, K. Helmy, S.S. Pattwell, K.L. Pitter, Q. LaPlant, T. Ozawa, E. C. Holland, In vivo radiation response of proneural glioma characterized by protective p53 transcriptional program and proneural-mesenchymal shift, Proc. Natl. Acad. Sci. U. S. A. 111 (2014) 5248–5253.
[52] T. Kalmar, C. Lim, P. Hayward, S. Muñoz-Descalzo, J. Nichols, J. Garcia-Ojalvo, A. Martinez Arias, Regulated fluctuations in nanog expression mediate cell fate decisions in embryonic stem cells, PLoS Biol. 7 (2009), e1000149.
[53] B.I. Gerashchenko, K. Salmina, J. Eglitis, A. Huna, V. Grjunberga, J. Erenpreisa, Disentangling the aneuploidy and senescence paradoxes: a study of triploid breast cancers non-responsive to neoadjuvant therapy, Histochem. Cell Biol. 145 (2016) 497–508.
[54] Y. Arima, N. Hayashi, H. Hayashi, M. Sasaki, K. Kai, E. Sugihara, E. Abe, A. Yoshida, S. Mikami, S. Nakamura, H. Saya, Loss of p16 expression is associated with the stem cell characteristics of surface markers and therapeutic resistance in estrogen receptor-negative breast cancer, Int. J. Cancer 130 (2012) 2568–2579.
[55] B.I. Gerashchenko, K. Salmina, J. Krigerts, J. Erenpreisa, A.M. Babsky, Induced polyploidy and sorting of damaged dna by micronucleation in radioresistant rat liver epithelial stem-like cells exposed to x-rays, Probl. Med. Radiobiol. 24 (2019) 220–234.
[56] P.-E. Puig, M.-N. Guilly, A. Bouchot, N. Droin, D. Cathelin, F. Bouyer, L. Favier, F. Ghiringhelli, G. Kroemer, E. Solary, F. Martin, B. Chauffert, Tumor cells can escape DNA-damaging cisplatin through DNA endoreduplication and reversible polyploidy, Cell Biol. Int. 32 (2008) 1031–1043.
[57] C. Leikam, A.L. Hufnagel, C. Otto, D.J. Murphy, B. Mühling, S. Kneitz, I. Nanda, M. Schmid, T.U. Wagner, S. Haferkamp, E.-B. Bröcker, M. Schartl, S. Meierjohann, In vitro evidence for senescent multinucleated melanocytes as a source for tumor-initiating cells, Cell Death Dis. 6 (2015) e1711.
[58] Y. Yu, K. Schleich, B. Yue, S. Ji, P. Lohneis, K. Kemper, M.R. Silvis, N. Qutob, E. van Rooijen, M. Werner-Klein, L. Li, D. Dhawan, S. Meierjohann, M. Reimann, A. Elkahloun, S. Treitschke, B. Dörken, C. Speck, F.A. Mallette, L.I. Zon, S. L. Holmen, D.S. Peeper, Y. Samuels, C.A. Schmitt, S. Lee, Targeting the senescence-overriding cooperative activity of structurally unrelated H3K9 demethylases in melanoma, Cancer Cell 33 (2018) 785.
[59] Y. Buganim, D.A. Faddah, R. Jaenisch, Mechanisms and models of somatic cell reprogramming, Nat. Rev. Genet. 14 (2013) 427–439, https://doi.org/10.1038/nrg3473.
[60] N. Malaquin, A. Martinez, F. Rodier, Keeping the senescence secretome under control: molecular reins on the senescence-associated secretory phenotype, Exp. Gerontol. 82 (2016) 39–49.
[61] A.N. Gorban, T.A. Tyukina, E.V. Smirnova, L.I. Pokidysheva, Evolution of adaptation mechanisms: Adaptation energy, stress, and oscillating death, J. Theor. Biol. 405 (2016) 127–139.
[62] J. Erenpreisa, K. Salmiņa, A. Belyayev, I. Inashkina, M.S. Cragg, Survival at the brink: chromatin autophagy of tumor cells in response to genotoxic challenge, in: M.A. Hayat (Ed.), Autophagy: Cancer, Other Pathologies, Inflammation, Immunity, Infection, and Aging, Academic Press, 2018, pp. 275–294.
[63] C.H. Lineweaver, P. Davies, Comparison of the atavistic model of cancer to somatic mutation theory: phylostratigraphic analyses support the atavistic model, in: B.S. Gerstman (Ed.), The Physics of Cancer: Research Advances, World Scientific, 2020, pp. 243–261.
[64] L. Hayflick, P.S. Moorhead, The serial cultivation of human diploid cell strains, Exp. Cell Res. 25 (1961) 585–621.
[65] J. Erenpreisa, M.S. Cragg, Cancer: a matter of life cycle? Cell Biol. Int. 31 (2007) 1507–1510.
[66] J. Erenpreisa, M.S. Cragg, Life-cycle features of tumour cells, in: P. Pontarotti (Ed.), Evolutionary Biology from Concept to Application, Springer Berlin Heidelberg, Berlin, Heidelberg, 2008, pp. 61–71.
[67] A. Weismann, Prof. Weismann's Theory of Heredity, Nature 41 (1890) 317–323.
[68] A.S. Kondrashov, Evolutionary genetics of life cycles, Annu. Rev. Ecol. Syst. 28 (1997) 391–435.
[69] A.E. Vinogradov, Human transcriptome nexuses: basic-eukaryotic and metazoan, Genomics. 95 (2010) 345–354.
[70] A.E. Vinogradov, O.V. Anatskaya, Evolutionary framework of the human interactome: unicellular and multicellular giant clusters, Biosystems 181 (2019) 82–87.
[71] T. Domazet-Lošo, D. Tautz, Phylostratigraphic tracking of cancer genes suggests a link to the emergence of multicellularity in metazoa, BMC Biol. 8 (2010), https://doi.org/10.1186/1741-7007-8-66.
[72] A.S. Trigos, R.B. Pearson, A.T. Papenfuss, D.L. Goode, Altered interactions between unicellular and multicellular genes drive hallmarks of transformation in a diverse range of solid tumors, Proc. Natl. Acad. Sci. U. S. A. 114 (2017) 6406–6411.
[73] A.S. Trigos, R.B. Pearson, A.T. Papenfuss, D.L. Goode, How the evolution of multicellularity set the stage for cancer, Br. J. Cancer 118 (2018) 145–152.
[74] A.S. Trigos, R.B. Pearson, A.T. Papenfuss, D.L. Goode, Somatic mutations in early metazoan genes disrupt regulatory links between unicellular and multicellular genes in cancer, Elife. 8 (2019), https://doi.org/10.7554/eLife.40947.
[75] S. Yildirim, S. Huang, Atavism: Accessing Ancient Attractors Hidden in the Epigenetic Landscape, Org. Divers. Evol. 2 (2018) 59–80.
[76] T.M. Illidge, M.S. Cragg, B. Fringes, P. Olive, J.A. Erenpreisa, Polyploid giant cells provide a survival mechanism for p53 mutant cells after DNA damage, Cell Biol. Int. 24 (2000) 621–633.
[77] J. Erenpreisa, M.S. Cragg, Three steps to the immortality of cancer cells: senescence, polyploidy and self-renewal, Cancer Cell Int. 13 (2013) 92.
[78] R. Mirzayans, B. Andrais, D. Murray, Roles of Polyploid/Multinucleated giant Cancer cells in metastasis and disease relapse following anticancer treatment, Cancers 10 (2018), https://doi.org/10.3390/cancers10040118.
[79] S.R. Amend, G. Torga, K.-C. Lin, L.G. Kostecka, A. de Marzo, R.H. Austin, K. J. Pienta, Polyploid giant cancer cells: unrecognized actuators of tumorigenesis, metastasis, and resistance, Prostate 79 (2019) 1489–1497.

[80] J. Chen, N. Niu, J. Zhang, L. Qi, W. Shen, K.V. Donkena, Z. Feng, J. Liu*, Polyploid giant cancer cells (PGCCs): the evil roots of Cancer, Curr. Cancer Drug Targets 19 (2019) 360–367.
[81] F. Kou, L. Wu, X. Ren, L. Yang, Chromosome abnormalities: new insights into their clinical significance in cancer, Mol. Ther. Oncolytics 17 (2020) 562–570.
[82] L. Comai, The advantages and disadvantages of being polyploid, Nat. Rev. Genet. 6 (2005) 836–846.
[83] S.P. Otto, The evolutionary consequences of polyploidy, Cell. 131 (2007) 452–462, https://doi.org/10.1016/j.cell.2007.10.022.
[84] Y. Van de Peer, E. Mizrachi, K. Marchal, The evolutionary significance of polyploidy, Nat. Rev. Genet. 18 (2017) 411–424.
[85] S. Ohno, Evolution by Gene Duplication, Springer Science & Business Media, 2013.
[86] D.T. Fox, D.E. Soltis, P.S. Soltis, T.-L. Ashman, Y. Van de Peer, Polyploidy: A Biological Force From Cells to Ecosystems, Trends Cell Biol. 30 (2020) 688–694.
[87] A.M. Nedelcu, O. Marcu, R.E. Michod, Sex as a response to oxidative stress: a twofold increase in cellular reactive oxygen species activates sex genes, Proc. Biol. Sci. 271 (2004) 1591–1596.
[88] A.S. Kondrashov, The asexual ploidy cycle and the origin of sex, Nature 370 (1994) 213–216.
[89] H. Bernstein, H.C. Byerly, F.A. Hopf, R.E. Michod, DNA Repair and Complementation: the Major Factors in the Origin and Maintenance of Sex, in``Origin and Evolution of Sex''(HO Halvorsen, Ed.), 1985.
[90] A.S. Kondrashov, Deleterious mutations as an evolutionary factor. 1. The advantage of recombination, Genet. Res. 44 (1984) 199–217.
[91] L.R. Cleveland, The origin and evolution of meiosis, Science 105 (1947) 287–289, https://doi.org/10.1126/science.105.2724.287.
[92] I.B. Raikov, The Protozoan Nucleus–morphology and Evolution, Springer-Verlag, 1982.
[93] J. Erenpreisa, M. Kalejs, M.S. Cragg, Mitotic catastrophe and endomitosis in tumour cells: an evolutionary key to a molecular solution, Cell Biol. Int. 29 (2005) 1012–1018.
[94] L. Yant, J.D. Hollister, K.M. Wright, B.J. Arnold, J.D. Higgins, F.C.H. Franklin, K. Bomblies, Meiotic adaptation to genome duplication in Arabidopsis arenosa, Curr. Biol. 23 (2013) 2151–2156.
[95] M. Freeling, Picking up the Ball at the K/Pg boundary: the distribution of ancient polyploidies in the plant phylogenetic tree as a spandrel of asexuality with occasional sex, Plant Cell 29 (2017) 202–206.
[96] A.V. Markov, I.S. Kaznacheev, Evolutionary consequences of polyploidy in prokaryotes and the origin of mitosis and meiosis, Biol. Direct 11 (2016), https://doi.org/10.1186/s13062-016-0131-8.
[97] X. Qiao, Q. Li, H. Yin, K. Qi, L. Li, R. Wang, S. Zhang, A.H. Paterson, Gene duplication and evolution in recurring polyploidization–diploidization cycles in plants, Genome Biol. 20 (2019) 38.
[98] N.M. Vainshelbaum, P. Zayakin, R. Kleina, A. Giuliani, J. Erenpreisa, Meta-Analysis of Cancer Triploidy: Rearrangements of Genome Complements in Male Human Tumors Are Characterized by XXY Karyotypes, Genes 10 (2019), https://doi.org/10.3390/genes10080613.
[99] K. Salmina, B.I. Gerashchenko, M. Hausmann, N.M. Vainshelbaum, P. Zayakin, J. Erenpreiss, T. Freivalds, M.S. Cragg, J. Erenpreisa, When three isn't a crowd: a digyny concept for treatment-resistant, near-triploid human cancers, Genes 10 (2019), https://doi.org/10.3390/genes10070551.
[100] S. Schulze, I. Petersen, Gender and ploidy in cancer survival, Cell. Oncol. 34 (2011) 199–208, https://doi.org/10.1007/s13402-011-0013-0.
[101] V.W. Mayer, A. Aguilera, High levels of chromosome instability in polyploids of Saccharomyces cerevisiae, Mutat. Res. 231 (1990) 177–186.
[102] B. McClintock, The stability of broken ends of chromosomes in Zea Mays, Genetics. 26 (1941) 234–282.
[103] D. Gisselsson, Chromosomal instability in cancer: causes and consequences, Atlas Genet, Cytogenet. Oncol. Haematol. (2001), https://doi.org/10.4267/2042/37771.
[104] L. Yant, K. Bomblies, Genome management and mismanagement—cell-level opportunities and challenges of whole-genome duplication, Genes Dev. 29 (2015) 2405–2419.
[105] K. Salmina, A. Huna, M. Kalejs, D. Pjanova, H. Scherthan, M.S. Cragg, J. Erenpreisa, The Cancer aneuploidy paradox: in the light of evolution, Genes 10 (2019), https://doi.org/10.3390/genes10020083.
[106] O.V. Anatskaya, A.E. Vinogradov, Somatic polyploidy promotes cell function under stress and energy depletion: evidence from tissue-specific mammal transcriptome, Funct. Integr. Genomics 10 (2010) 433–446.
[107] T.L. Orr-Weaver, When bigger is better: the role of polyploidy in organogenesis, Trends Genet. 31 (2015) 307–315.
[108] W.Y. Brodsky, I.V. Uryvaeva, Cell polyploidy: its relation to tissue growth and function, Int. Rev. Cytol. 50 (1977) 275–332.
[109] W. Nagl, Polyploidy in differentiation and evolution, Int. J. Cell Cloning 8 (1990) 216–223.
[110] B.N. Kudryavtsev, M.V. Kudryavtseva, G.A. Sakuta, G.I. Stein, Human hepatocyte polyploidization kinetics in the course of life cycle, Virchows Arch, B Cell Pathol. Incl. Mol. Pathol. 64 (1993) 387–393.
[111] K.A. Knouse, J. Wu, C.A. Whittaker, A. Amon, Single cell sequencing reveals low levels of aneuploidy across mammalian tissues, Proc. Natl. Acad. Sci. U. S. A. 111 (2014) 13409–13414.
[112] J. Grendler, S. Lowgren, M. Mills, V.P. Losick, Wound-induced polyploidization is driven by Myc and supports tissue repair in the presence of DNA damage, Development. 146 (2019), https://doi.org/10.1242/dev.173005.
[113] J. Erenpreisa, A. Giuliani, A.E. Vinogradov, O.V. Anatskaya, A. Vazquez-Martin, K. Salmina, M.S. Cragg, Stress-induced polyploidy shifts somatic cells towards a pro-tumourogenic unicellular gene transcription network, Cancer Hypotheses. 1 (2018) 1–20.
[114] O.V. Anatskaya, A.E. Vinogradov, N.M. Vainshelbaum, A. Giuliani, J. Erenpreisa, Phylostratic shift of whole-genome duplications in normal mammalian tissues towards unicellularity is driven by developmental bivalent genes and reveals a link to Cancer, Int. J. Mol. Sci. 21 (2020), https://doi.org/10.3390/ijms21228759.
[115] A. Vazquez-Martin, O.V. Anatskaya, A. Giuliani, J. Erenpreisa, S. Huang, K. Salmina, I. Inashkina, A. Huna, N.N. Nikolsky, A.E. Vinogradov, Somatic polyploidy is associated with the upregulation of c-MYC interacting genes and EMT-like signature, Oncotarget. 7 (2016) 75235–75260.
[116] V. Poli, L. Fagnocchi, A. Fasciani, A. Cherubini, S. Mazzoleni, S. Ferrillo, A. Miluzio, G. Gaudioso, V. Vaira, A. Turdo, M. Gaggianesi, A. Chinnici, E. Lipari, S. Bicciato, S. Bosari, M. Todaro, A. Zippo, MYC-driven epigenetic reprogramming favors the onset of tumorigenesis by inducing a stem cell-like state, Nat. Commun. 9 (2018) 1024.
[117] Q. Li, C.V. Dang, c-Myc overexpression uncouples DNA replication from mitosis, Mol. Cell. Biol. 19 (1999) 5339–5351.
[118] P.B. Rahl, C.Y. Lin, A.C. Seila, R.A. Flynn, S. McCuine, C.B. Burge, P.A. Sharp, R. A. Young, c-Myc regulates transcriptional pause release, Cell. 141 (2010) 432–445.
[119] B.E. Bernstein, T.S. Mikkelsen, X. Xie, M. Kamal, D.J. Huebert, J. Cuff, B. Fry, A. Meissner, M. Wernig, K. Plath, R. Jaenisch, A. Wagschal, R. Feil, S.L. Schreiber, E.S. Lander, A bivalent chromatin structure marks key developmental genes in embryonic stem cells, Cell. 125 (2006) 315–326.
[120] F. Court, P. Arnaud, An annotated list of bivalent chromatin regions in human ES cells: a new tool for cancer epigenetic research, Oncotarget. 8 (2017) 4110–4124.
[121] H.-S. Sin, A.V. Kartashov, K. Hasegawa, A. Barski, S.H. Namekawa, Poised chromatin and bivalent domains facilitate the mitosis-to-meiosis transition in the male germline, BMC Biol. 13 (2015) 53.
[122] S.H. Bernhart, H. Kretzmer, L.M. Holdt, F. Jühling, O. Ammerpohl, A. K. Bergmann, B.H. Northoff, G. Doose, R. Siebert, P.F. Stadler, S. Hoffmann, Changes of bivalent chromatin coincide with increased expression of developmental genes in cancer, Sci. Rep. 6 (2016) 37393.
[123] A.J. Faure, J.M. Schmiedel, B. Lehner, Systematic analysis of the determinants of gene expression noise in embryonic stem cells, Cell Syst. 5 (2017), 471–484.e4.
[124] B.D. MacArthur, I.R. Lemischka, Statistical mechanics of pluripotency, Cell. 154 (2013) 484–489.
[125] M.D. Vincent, Cancer: beyond speciation, Adv. Cancer Res. 112 (2011) 283–350.
[126] P.C.W. Davies, C.H. Lineweaver, Cancer tumors as Metazoa 1.0: tapping genes of ancient ancestors, Phys. Biol. 8 (2011), 015001.
[127] C.H. Lineweaver, P.C.W. Davies, M.D. Vincent, Targeting cancer's weaknesses (not its strengths): therapeutic strategies suggested by the atavistic model, Bioessays. 36 (2014) 827–835.
[128] J. Cohnheim, Vorlesungen über allgemeine Pathologie : Handbuch für Ärzte und Studierende, Hirschwald, Berlin, 1877-1880.
[129] J.O. Erenpreiss, Current Concepts of Malignant Growth, Zinatne Publ, Riga, 1993.
[130] L.P. Bignold, B.L.D. Coghlan, H.P.A. Jersmann, Boveri Hansemann, Hansemann, Boveri, chromosomes and the gametogenesis-related theories of tumours, Cell Biol. Int. 30 (2006) 640–644.
[131] V. Vinnitsky, The development of a malignant tumor is due to a desperate asexual self-cloning process in which cancer stem cells develop the ability to mimic the genetic program of germline cells, Intrinsically Disord. Proteins 2 (2014) e29997, https://doi.org/10.4161/idp.29997.
[132] J. Erenpreisa, K. Salmina, A. Huna, T.R. Jackson, A. Vazquez-Martin, M.S. Cragg, The "virgin birth", polyploidy, and the origin of cancer, Oncoscience 2 (2015) 3–14.
[133] N. Niu, I. Mercado-Uribe, J. Liu, Dedifferentiation into blastomere-like cancer stem cells via formation of polyploid giant cancer cells, Oncogene 36 (2017) 4887–4900.
[134] K. Illmensee, B. Mintz, Totipotency and normal differentiation of single teratocarcinoma cells cloned by injection into blastocysts, Proc. Natl. Acad. Sci. U. S. A. 73 (1976) 549–553.
[135] R.H. Blelloch, K. Hochedlinger, Y. Yamada, C. Brennan, M. Kim, B. Mintz, L. Chin, R. Jaenisch, Nuclear cloning of embryonal carcinoma cells, Proc. Natl. Acad. Sci. U. S. A. 101 (2004) 13985–13990.
[136] G.B. Pierce, Carcinoma is to embryology as mutation is to genetics, Am. Zool. 25 (1985) 707–712.
[137] D. Muñoz-Espín, M. Cañamero, A. Maraver, G. Gómez-López, J. Contreras, S. Murillo-Cuesta, A. Rodríguez-Baeza, I. Varela-Nieto, J. Ruberte, M. Collado, M. Serrano, Programmed cell senescence during mammalian embryonic development, Cell. 155 (2013) 1104–1118.
[138] M. Storer, A. Mas, A. Robert-Moreno, M. Pecoraro, M.C. Ortells, V. Di Giacomo, R. Yosef, N. Pilpel, V. Krizhanovsky, J. Sharpe, W.M. Keyes, Senescence is a developmental mechanism that contributes to embryonic growth and patterning, Cell. 155 (2013) 1119–1130.
[139] D.H. Ledbetter, Chaos in the embryo, Nat. Med. 15 (2009) 490–491.
[140] E. Vanneste, T. Voet, C. Le Caignec, M. Ampe, P. Konings, C. Melotte, S. Debrock, M. Amyere, M. Vikkula, F. Schuit, J.-P. Fryns, G. Verbeke, T. D'Hooghe, Y. Moreau, J.R. Vermeesch, Chromosome instability is common in human cleavage-stage embryos, Nat. Med. 15 (2009) 577–583.
[141] A.E. Peaston, B.B. Knowles, K.W. Hutchison, Genome plasticity in the mouse oocyte and early embryo, Biochem. Soc. Trans. 35 (2007) 618–622.

[142] S. Zhang, I. Mercado-Uribe, Z. Xing, B. Sun, J. Kuang, J. Liu, Generation of cancer stem-like cells through the formation of polyploid giant cancer cells, Oncogene. 33 (2014) 116–128.
[143] Z. Weihua, Q. Lin, A.J. Ramoth, D. Fan, I.J. Fidler, Formation of solid tumors by a single multinucleated cancer cell, Cancer 117 (2011) 4092–4099.
[144] J. Liu, The "life code": a theory that unifies the human life cycle and the origin of human tumors, Semin. Cancer Biol. 60 (2020) 380–397.
[145] D. Díaz-Carballo, S. Gustmann, H. Jastrow, A.H. Acikelli, P. Dammann, J. Klein, U. Dembinski, W. Bardenheuer, S. Malak, M.J. Araúzo-Bravo, B. Schultheis, C. Aldinger, D. Strumberg, Atypical cell populations associated with acquired resistance to cytostatics and cancer stem cell features: the role of mitochondria in nuclear encapsulation, DNA Cell Biol. 33 (2014) 749–774.
[146] Y. Zhang, Cancer embryonic stem cell-like attractors alongside deficiency of regulatory restraints of cell-division and cell-cycle, J. Genet. Syndr. Gene Ther. 4 (2013) 2.
[147] S.K. Zaidi, S.E. Frietze, J.A. Gordon, J.L. Heath, T. Messier, D. Hong, J.R. Boyd, M. Kang, A.N. Imbalzano, J.B. Lian, J.L. Stein, G.S. Stein, Bivalent epigenetic control of oncofetal gene expression in Cancer, Mol. Cell. Biol. 37 (2017), https://doi.org/10.1128/MCB.00352-17.
[148] H.-L. Zhang, P. Wang, M.-Z. Lu, S.-D. Zhang, L. Zheng, c-Myc maintains the self-renewal and chemoresistance properties of colon cancer stem cells, Oncol. Lett. 17 (2019) 4487–4493.
[149] C. Nielsen, Animal Evolution : Interrelationships of the Living Phyla, OUP Oxford, 2001.
[150] K. Nishimura, S. Watanabe, R. Hayashida, S. Sugishima, T. Iwasaka, T. Kaku, Binucleated HeLa cells are formed by cytokinesis failure in starvation and keep the potential of proliferation, Cytotechnology. 68 (2016) 1123–1130.
[151] J. Erenpreisa, M. Kalejs, F. Ianzini, E.A. Kosmacek, M.A. Mackey, D. Emzinsh, M. S. Cragg, A. Ivanov, T.M. Illidge, Segregation of genomes in polyploid tumour cells following mitotic catastrophe, Cell Biol. Int. 29 (2005) 1005–1011.
[152] F. Ianzini, E.A. Kosmacek, E.S. Nelson, E. Napoli, J. Erenpreisa, M. Kalejs, M. A. Mackey, Activation of meiosis-specific genes is associated with depolyploidization of human tumor cells following radiation-induced mitotic catastrophe, Cancer Res. 69 (2009) 2296–2304.
[153] K.H. Walen, Mitotic Slippage Process Concealed Cancer-Sought Chromosome Instability Mechanism (S-CIN), J. Cancer Ther. 8 (2017) 608–623.
[154] T. Davoli, E.L. Denchi, T. de Lange, Persistent telomere damage induces bypass of mitosis and tetraploidy, Cell. 141 (2010) 81–93.
[155] T. Davoli, T. de Lange, Telomere-driven tetraploidization occurs in human cells undergoing crisis and promotes transformation of mouse cells, Cancer Cell 21 (2012) 765–776.
[156] J. Erenpreisa, M.S. Cragg, MOS, aneuploidy and the ploidy cycle of cancer cells, Oncogene. 29 (2010) 5447–5451.
[157] K. Salmina, A. Bojko, I. Inashkina, K. Staniak, M. Dudkowska, P. Podlesniy, F. Rumnieks, N.M. Vainshelbaum, D. Pjanova, E. Sikora, J. Erenpreisa, "Mitotic slippage" and extranuclear DNA in Cancer chemoresistance: a focus on telomeres, Int. J. Mol. Sci. 21 (2020) 2779.
[158] C. Mantel, Y. Guo, M.R. Lee, M.K. Han, S. Rhorabough, K.S. Kim, H.E. Broxmeyer, Cells enter a unique intermediate 4N stage, not 4N-G1, after aborted mitosis, Cell Cycle 7 (2008) 484–492.
[159] J. Erenpreisa, K. Salmina, A. Huna, E.A. Kosmacek, M.S. Cragg, F. Ianzini, A. P. Anisimov, Polyploid tumour cells elicit paradiploid progeny through depolyploidizing divisions and regulated autophagic degradation, Cell Biol. Int. 35 (2011) 687–695.
[160] J. Erenpreisa, M.S. Cragg, A.P. Anisimov, T.M. Illidge, Tumor cell embryonality and the ploidy number 32n: is it a developmental checkpoint? Cell Cycle 10 (2011) 1873–1874.
[161] J. Erenpreisa, M. Cragg, B. Fringes, I. Sharakhov, T.M. Illidge, Release of mitotic descendants by giant cells from irradiated burkitt's lymphoma cell lines, Cell Biol. Int. 24 (2000) 635–648, https://doi.org/10.1006/cbir.2000.0558.
[162] K.H. Walen, Spindle apparatus uncoupling in endo-tetraploid asymmetric division of stem and non-stem cells, Cell Cycle 8 (2009) 3234–3237.
[163] K.H. Walen, Neoplastic-like Cell Changes of Normal Fibroblast Cells Associated With Evolutionary Conserved Maternal and Paternal Genomic Autonomous Behavior (Gonomery), J. Cancer Ther. 2014 (2014). https://www.scirp.org/html/5-8901972_49182.htm.
[164] J. Erenpreisa, M.S. Cragg, K. Salmina, M. Hausmann, H. Scherthan, The role of meiotic cohesin REC8 in chromosome segregation in gamma irradiation-induced endopolyploid tumour cells, Exp. Cell Res. 315 (2009) 2593–2603.
[165] K. Salmina, E. Jankevics, A. Huna, D. Perminov, I. Radovica, T. Klymenko, A. Ivanov, E. Jascenko, H. Scherthan, M. Cragg, J. Erenpreisa, Up-regulation of the embryonic self-renewal network through reversible polyploidy in irradiated p53-mutant tumour cells, Exp. Cell Res. 316 (2010) 2099–2112.
[166] C. Lagadec, E. Vlashi, L. Della Donna, C. Dekmezian, F. Pajonk, Radiation-induced reprogramming of breast Cancer cells, Stem Cells 30 (2012) 833–844, https://doi.org/10.1002/stem.1058.
[167] A. Ivanov, M.S. Cragg, J. Erenpreisa, D. Emzinsh, H. Lukman, T.M. Illidge, Endopolyploid cells produced after severe genotoxic damage have the potential to repair DNA double strand breaks, J. Cell. Sci. 116 (2003) 4095–4106.
[168] G. Mosieniak, E. Sikora, Polyploidy: the link between senescence and cancer, Curr. Pharm. Des. 16 (2010) 734–740.
[169] S. Rello-Varona, D. Lissa, S. Shen, M. Niso-Santano, L. Senovilla, G. Mariño, I. Vitale, M. Jemaá, F. Harper, G. Pierron, M. Castedo, G. Kroemer, Autophagic removal of micronuclei, Cell Cycle 11 (2012) 170–176.
[170] D. Pjanova, N.M. Vainshelbaum, K. Salmina, J. Erenpreisa, The role of the meiotic component in reproduction of B-RAF-Mutated melanoma: a review and "Brainstorming" session, Melanoma Res. (2020). https://www.intechopen.com/online-first/the-role-of-the-meiotic-component-in-reproduction-of-b-raf-mutated-melanoma-a-review-and-brainstormi.
[171] M. Kalejs, J. Erenpreisa, Cancer/testis antigens and gametogenesis: a review and "brain-storming" session, Cancer Cell Int. 5 (2005) 4.
[172] M. Kalejs, A. Ivanov, G. Plakhins, M.S. Cragg, D. Emzinsh, T.M. Illidge, J. Erenpreisa, Upregulation of meiosis-specific genes in lymphoma cell lines following genotoxic insult and induction of mitotic catastrophe, BMC Cancer 6 (2006) 6.
[173] L.J. Old, Cancer is a somatic cell pregnancy, Cancer Immun. 7 (2007) 19.
[174] I. Vitale, L. Senovilla, M. Jemaà, M. Michaud, L. Galluzzi, O. Kepp, L. Nanty, A. Criollo, S. Rello-Varona, G. Manic, D. Métivier, S. Vivet, N. Tajeddine, N. Joza, A. Valent, M. Castedo, G. Kroemer, Multipolar mitosis of tetraploid cells: inhibition by p53 and dependency on Mos, EMBO J. 29 (2010) 1272–1284.
[175] S.F. Lindsey, D.M. Byrnes, M.S. Eller, A.M. Rosa, N. Dabas, J. Escandon, J. M. Grichnik, Potential role of meiosis proteins in melanoma chromosomal instability, J. Skin Cancer 2013 (2013), 190109.
[176] J.W. Bruggeman, J. Koster, P. Lodder, S. Repping, G. Hamer, Massive expression of germ cell-specific genes is a hallmark of cancer and a potential target for novel treatment development, Oncogene. 37 (2018) 5694–5700.
[177] A.M. Rosa, N. Dabas, D.M. Byrnes, M.S. Eller, J.M. Grichnik, Germ cell proteins in melanoma: prognosis, diagnosis, treatment, and theories on expression, J. Skin Cancer 2012 (2012), 621968.
[178] J. Feichtinger, R.J. McFarlane, Meiotic gene activation in somatic and germ cell tumours, Andrology. 7 (2019) 415–427.
[179] J. Gantchev, A. Martínez Villarreal, S. Gunn, M. Zetka, N. Ødum, I.V. Litvinov, The ectopic expression of meiCT genes promotes meiomitosis and may facilitate carcinogenesis, Cell Cycle 19 (2020) 837–854.
[180] N. Niu, J. Zhang, N. Zhang, I. Mercado-Uribe, F. Tao, Z. Han, S. Pathak, A. S. Multani, J. Kuang, J. Yao, R.C. Bast, A.K. Sood, M.-C. Hung, J. Liu, Linking genomic reorganization to tumor initiation via the giant cell cycle, Oncogenesis. 5 (2016) e281.
[181] S. Fais, M. Overholtzer, Cell-in-cell phenomena in cancer, Nat. Rev. Cancer 18 (2018) 758–766.
[182] B. Xuan, D. Ghosh, E.M. Cheney, E.M. Clifton, M.R. Dawson, Dysregulation in actin cytoskeletal organization drives increased stiffness and migratory persistence in polyploidal giant Cancer cells, Sci. Rep. 8 (2018) 11935.
[183] V.F. Niculescu, The cancer stem cell family: atavistic origin and tumorigenic development, MOJ Tumor Res. 1 (2018) 71–74.
[184] V.F. Niculescu, aCLS cancers: genomic and epigenetic changes transform the cell of origin of cancer into a tumorigenic pathogen of unicellular organization and lifestyle, Gene. 726 (2020), 144174.
[185] A.V. Goodkov, M.A. Berdieva, Y.I. Podlipaeva, S.Y. Demin, The chromatin extrusion phenomenon in Amoeba proteus cell cycle, J. Eukaryot, Microbiol. 67 (2020) 203–208.
[186] M. Berdieva, S. Demin, A. Goodkov, Amoeba proteus and ploidy cycles: from simple model to complex issues, Protistology. 13 (2019) 166–173.
[187] S.Y. Demin, S.Yu. Demin, M.A. Berdieva, A.V. Goodkov, Cyclic polyploidy in obligate agamic amoebae, Cell tissue biol. 13 (2019) 242–246, https://doi.org/10.1134/s1990519x19030027.
[188] M. Sundaram, D.L. Guernsey, M.M. Rajaraman, R. Rajaraman, Neosis: a novel type of cell division in cancer, Cancer Biol. Ther. 3 (2004) 207–218.
[189] K. Walen, Normal human cells acquiring proliferative advantage to hyperplasia-like growth-morphology: aberrant progeny cells associated with endopolyploid and haploid divisions, Oncol. 2 (2013) 19.
[190] R. Rajaraman, D.L. Guernsey, M.M. Rajaraman, S.R. Rajaraman, Neosis - a parasexual somatic reduction division in Cancer, Int. J. Hum. Genet. 7 (2007) 29–48.
[191] J. Leblanc, X. Zhang, D. McKee, Z.-B. Wang, R. Li, C. Ma, Q.-Y. Sun, X.J. Liu, The small GTPase Cdc42 promotes membrane protrusion during polar body emission via ARP2-nucleated actin polymerization, Mol. Hum. Reprod. 17 (2011) 305–316.
[192] S.-C. Sun, Q.-Y. Sun, N.-H. Kim, JMY is required for asymmetric division and cytokinesis in mouse oocytes, Mol. Hum. Reprod. 17 (2011) 296–304.
[193] D. Poccia, Developmental biology. eighth edition. by scott f gilbert; with a chapter on plant development by, susan r singer. sunderland (Massachusetts): sinauer associates. $112.95. xix 817 p; ill.; author and subject indexes. ISBN: 0–87893–250–X. [CD-ROM enclosed.] 2006, Q. Rev. Biol. 81 (2006), https://doi.org/10.1086/511569, 400–400.
[194] J.X. Zhou, L. Cisneros, T. Knijnenburg, K. Trachana, P. Davies, S. Huang, Phylostratigraphic analysis of tumor and developmental transcriptomes reveals relationship between oncogenesis, phylogenesis and ontogenesis, Converg. Sci. Phys. Oncol. (2018), https://doi.org/10.1101/199083.
[195] H. Lin, A.C. Spradling, Germline stem cell division and egg chamber development in transplanted Drosophila germaria, Dev. Biol. 159 (1993) 140–152.
[196] K. McCall, Eggs over easy: cell death in the Drosophila ovary, Dev. Biol. 274 (2004) 3–14.
[197] G. Prieur-Carrillo, K. Chu, J. Lindqvist, W.C. Dewey, Computerized video time-lapse (CVTL) analysis of the fate of giant cells produced by X-irradiating EJ30 human bladder carcinoma cells, Radiat. Res. 159 (2003) 705–712.
[198] T.G. Zybina, E.V. Zybina, Role of cell cycling and polyploidy in placental trophoblast of different mammalian species, Reprod. Domest. Anim. (2020), https://doi.org/10.1111/rda.13732.
[199] J. Liu, The dualistic origin of human tumors, Semin. Cancer Biol. 53 (2018) 1–16.
[200] J. Wang, G.M.B. Veronezi, Y. Kang, M. Zagoskin, E.T. O'Toole, R.E. Davis, Comprehensive chromosome end remodeling during programmed DNA elimination, Curr. Biol. 30 (2020), 3397–3413.e4.

[201] T. Boveri, Ueber differenzierung der zellkerne wahrend der furchung des eies von Ascaris megalocephala, Anat. Anz. 2 (1887) 688–693.
[202] P.A. Hardy, H. Zacharias, Reappraisal of the Hansemann-Boveri hypothesis on the origin of tumors, Cell Biol, Int. 29 (2005) 983–992.
[203] J.M. Sheltzer, A. Amon, The aneuploidy paradox: costs and benefits of an incorrect karyotype, Trends Genet. 27 (2011) 446–453.
[204] D. Hanahan, R.A. Weinberg, Hallmarks of cancer: the next generation, Cell. 144 (2011) 646–674.
[205] J. Coward, A. Harding, Size does matter: why polyploid tumor cells are critical drug targets in the war on Cancer, Front. Oncol. 4 (2014) 123.
[206] H.H.Q. Heng, S.M. Regan, G. Liu, C.J. Ye, Why it is crucial to analyze non clonal chromosome aberrations or NCCAs? Mol. Cytogenet. 9 (2016) 15.
[207] H.H.Q. Heng, G. Liu, S. Bremer, K.J. Ye, J. Stevens, C.J. Ye, Clonal and non-clonal chromosome aberrations and genome variation and aberration, Genome. 49 (2006) 195–204.
[208] B.R. Mardin, A.P. Drainas, S.M. Waszak, J. Weischenfeldt, M. Isokane, A.M. Stütz, B. Raeder, T. Efthymiopoulos, C. Buccitelli, M. Segura-Wang, P. Northcott, S. M. Pfister, P. Lichter, J. Ellenberg, J.O. Korbel, A cell-based model system links chromothripsis with hyperploidy, Mol. Syst. Biol. 11 (2015) 828.
[209] M.L. Leibowitz, C.-Z. Zhang, D. Pellman, Chromothripsis: A New Mechanism for Rapid Karyotype Evolution, Annu. Rev. Genet. 49 (2015) 183–211.
[210] I. Cortés-Ciriano, J.J.-K. Lee, R. Xi, D. Jain, Y.L. Jung, L. Yang, D. Gordenin, L. J. Klimczak, C.-Z. Zhang, D.S. Pellman, PCAWG Structural Variation Working Group, P.J. Park, PCAWG Consortium, comprehensive analysis of chromothripsis in 2,658 human cancers using whole-genome sequencing, Nat. Genet. 52 (2020) 331–341.
[211] X. Zeng, W.K. Xu, T.M. Lok, H.T. Ma, R.Y.C. Poon, Imbalance of the spindle-assembly checkpoint promotes spindle poison-mediated cytotoxicity with distinct kinetics, Cell Death Dis. 10 (2019) 314.
[212] T.P. Szatrowski, C.F. Nathan, Production of large amounts of hydrogen peroxide by human tumor cells, Cancer Res. 51 (1991) 794–798.
[213] A. Kasperski, R. Kasperska, Bioenergetics of life, disease and death phenomena, Theory Biosci. 137 (2018) 155–168.
[214] A. Kaya, M. Mariotti, A. Tyshkovskiy, X. Zhou, M.L. Hulke, S. Ma, M. V. Gerashchenko, A. Koren, V.N. Gladyshev, Molecular signatures of aneuploidy-driven adaptive evolution, Nat. Commun. 11 (2020) 588.
[215] A.J. Holland, D.W. Cleveland, Losing balance: the origin and impact of aneuploidy in cancer, EMBO Rep. 13 (2012) 501–514.
[216] S.K. Maciver, Asexual amoebae escape Muller's ratchet through polyploidy, Trends Parasitol. 32 (2016) 855–862.
[217] S.K. Maciver, Z. Koutsogiannis, A. de Obeso Fernández Del Valle, Meiotic genes" are constitutively expressed in an asexual amoeba and are not necessarily involved in sexual reproduction, Biol. Lett. 15 (2019), 20180871.
[218] T. Hu, Y. Kumar, I. Shazia, S.-J. Duan, Y. Li, L. Chen, J.-F. Chen, R. Yin, A. Kwong, G.K.-K. Leung, W.-K. Mat, Z. Wu, X. Long, C.-H. Chan, S. Chen, P. Lee, S.-K. Ng, T. Y.C. Ho, J. Yang, X. Ding, S.-Y. Tsang, X. Zhou, D.-H. Zhang, International Cancer genome consortium, E.-X. Zhou, L. Xu, W.-S. Poon, H.-Y. Wang, H. Xue, forward and reverse mutations in stages of cancer development, Hum. Genomics 12 (2018) 40.
[219] Z. Meir, Z. Mukamel, E. Chomsky, A. Lifshitz, A. Tanay, Single-cell analysis of clonal maintenance of transcriptional and epigenetic states in cancer cells, Nat. Genet. 52 (2020) 709–718.