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Nicotinamide as a chemopreventive therapy of skin cancers. Too much of good thing ?

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Dear Editor: The high incidence of keratinocyte cancers globally makes a chemopreventive approach to inhibit development of new skin cancers attractive. Chen and colleagues reported the results of a phase III double blind, randomized, placebo controlled clinical trial showing that nicotinamide (NAM), an amide form of vitamin B3, leads to a reduction in the rates of new keratinocyte cancers in patients who previously had skin cancer (Chen et al., 2015) (Figure 1).

At a molecular level, NAM is converted to the biologically active nicotinamide adenine dinucleotide (NAD^+) through the salvage pathway, in which the phosphoribosyltransferase NAMPT is the rate-limiting enzyme. NAD^+ is a cofactor with roles in multiple key cellular

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processes and enzyme functions involved in DNA repair and anti-inflammatory response. In this way, NAD^+ precursors, may help to prevent cancer progression. As exposure to UV radiation causes development of both melanoma and keratinocyte cancers, the majority of individuals within the target populations for chemoprevention are at risk of both these types of neoplasia. Thus, the question of whether NAM could also be used as a chemopreventive agent for melanoma in high-risk populations was raised (Minocha et al., 2018).

This question is particularly important, in the light of recent reports showing that oncogenic $BRAF^{V600E}$ and ERK pathway activation increased NAMPT expression and cellular levels of NAD^+ in melanocyte and melanoma cells (Audrito et al., 2018; Ohanna et al., 2018). Likewise, increased NAMPT and NAD^+ levels favored melanoma cell motility and resistance to BRAF inhibitors (Figure 1). Finally, the decrease of NAD^+ levels following pharmacological NAMPT inhibition dampens the development of BRAFi sensitive and resistant melanoma tumors in vivo (Audrito et al., 2018; Ohanna et al., 2018). Because the beneficial effects of nicotinamide on skin cancer prevention may be due to immune modulatory phenomenon (Damian, 2017), it is worth noting that these studies were carried out in immune-compromised mice.

Hence, it seems warranted to be cautious when encouraging the use of NAD^+ precursors such as vitamin B3 or nicotinamide as a chemopreventive therapy of skin cancers, particularly in individuals at risk of melanoma because of germline mutations, familial or personal history of melanoma. The same precautions are required in those susceptible to skin carcinomas who may also develop melanoma, as NAM supplementation did not inhibit development of high-risk keratinocyte cancers (Nehal and Bichakjian, 2018). It also is conceivable that individuals prescribed vitamin supplements, convinced of their protective benefits, may be more prone to neglect measures against excessive sun exposure.

The fact that altered NAD^+ metabolism has been related to oncogenic signaling in various cancers suggests that, until more information is available, advocating nicotinamide for the prevention of keratinocyte cancers and/or melanoma may be premature at this stage. Indeed, there were more infiltrating/morphoeic basal cell carcinomas and poorly differentiated squamous cell carcinomas in the nicotinamide group than in the placebo group at 12-months in the Chen et al study (2015). Furthermore, new melanomas (with an even distribution between the two groups) were diagnosed during the 12-month intervention period and a non-significant trend toward the development of more squamous-cell carcinomas in the nicotinamide group than in the placebo group in the 6-month postintervention period was observed (Chen et al., 2015).

Overall, the role of NAM and NAD+ metabolism in skin cancer may be a double-edged sword, and further studies are warranted before clear guidance can be provided on the risks and benefits of NAM supplementation. As a more general consideration, it might be prudent for health professionals to raise awareness of the public over the potential dangers of the use of NAD+ precursors as dietary supplements that is becoming very trendy as an anti-ageing strategy.

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Conflicts of interest

The authors declare no conflicts of interest

Figure legends

Figure 1: Effect of nicotinamide metabolism on skin cancers. Nicotinamide (NAM), which is converted to NAD+, has DNA repair and anti-inflammatory properties. NAM was shown to prevent keratinocyte cancers in patients who previously had skin cancer. In melanocytes and melanoma cells, $BRAF^{V600E}$ mutation enhances NAMPT expression and the metabolism of NAD+, which in melanoma cells favors cell survival, motility and BRAF inhibitor-resistance.

Red boxes are therapeutic effects (left) or side-effects (right) that warrant further investigation.

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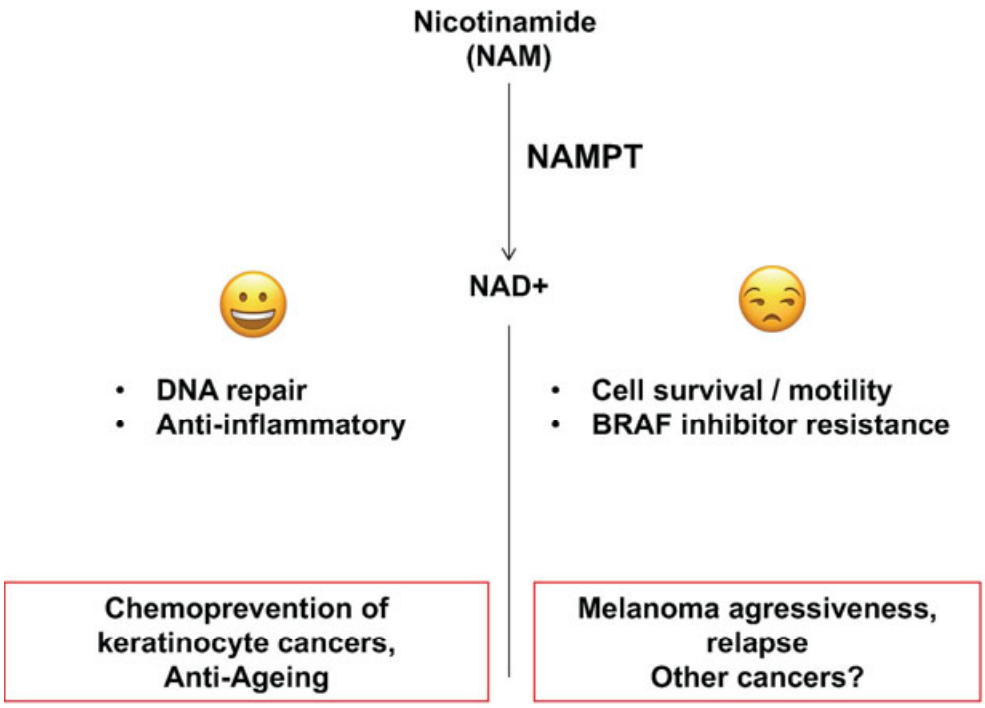

Figure1: Effect of nicotinamide metabolism on skin cancers. Nicotinamide (NAM), which is converted to NAD+, has DNA repair and anti-inflammatory properties. NAM was shown to prevent keratinocyte cancers in patients who previously had skin cancer. In melanocytes and melanoma cells, *BRAF*^{V600E} mutation enhances NAMPT expression and the metabolism of NAD+, which in melanoma cells favors cell survival, motility and BRAF inhibitor-resistance.
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