

Could anionic LDL be a ligand for RAGE and TREM2 in addition to LOX-1 and thus exacerbate lung disease and dementia?

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ABSTRACT

We recently highlighted the potential of protein glycation to generate anionic (electronegative) surfaces. We hypothesised that these anionic proteins are perceived by the innate immune system as arising from infection or damaged cell components, producing an inflammatory response within the lung involving the receptor RAGE. We now review two other pathologies linked to the innate immune response, cardiovascular disease and dementia that involve receptors LOX-1 and TREM2 respectively. Remarkable similarities in properties between RAGE, LOX-1 and TREM2 suggest that electronegative LDL may act as a pathogenic anionic ligand for all three receptors and exacerbate lung inflammation and dementia.

1. Introduction

We have previously highlighted the role of the human acute phase protein, group IIa PLA₂, as part of innate immunity [1,2]. This protein is highly cationic with a global distribution of positively charged arginine and lysine residues on its surface, allowing this phospholipase to bind to anionic structures including bacteria via non-specific electrostatic interactions. The positive charge is crucial for the group IIa PLA₂ to function as the changing of up to five positive residues on the surface of the protein to negative ones by charge reversal site directed mutagenesis leads to a loss of anti-bacterial function [3]. This recognition of anionic structures, such as pathogens or cell debris, by specific receptor proteins that express cationic patches on their surface is a fundamental aspect of innate immunity.

In a previous article [4], we hypothesised that COVID-19 morbidity and mortality may be the result of the activation of innate immunity, specifically involving the receptor for advanced glycation end products (RAGE) [5,6]. This receptor is constitutively expressed in lung epithelial cells. The basis of this hypothesis is that the process of protein glycation, through the chemical reaction with glucose and its carbonyl-containing metabolites, generates anionic protein surfaces. These more electronegative protein molecules are the result of the charge neutralization of positively-charged arginine and lysine residues on protein surfaces by a complex series of chemical (non-enzymatic) reactions (Maillard

reaction) [7,8]. More dramatically, the formation of a Schiff base between glucose and lysine can, with further chemical modifications [6,8], give rise to carboxymethyl lysine thus replacing a positive charge on the lysine with a negatively charged carboxylate group, an example of a charge reversal by chemical modification. The consequence of these changes is that negatively charged aspartate and glutamate residues on the protein surface together with the possible introduction of an additional negative charge will predominate, thus increasing the net negative charge of the protein. This will subsequently promote an innate immune response as these now anionic molecules are seen as being associated with infection (pathogen associated molecular pattern molecules; PAMPS) or cell damage (damage associated molecular pattern molecules; DAMPS). The latter phenomenon is referred to as sterile inflammation [9].

An innate response will attempt to remove these anionic macromolecules thus promoting a basal or low-grade inflammatory condition within the body. These anionic structures include Gram-positive bacteria, released RNA and apoptotic cells exposing negatively charged phosphatidyl serine. Removal of these non-self and altered-self targets by innate immune cells is mediated by cell surface scavenger receptors. Binding to scavenger receptors promotes the elimination of degraded or harmful substances by endocytosis, phagocytosis, adhesion or signalling [10].

The physiological and clinical importance of protein glycation from

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glucose and its carbonyl-containing metabolites is highlighted in diabetes where poor glycaemic control leads to cardiovascular and other problems. However, there is a lack of precise molecular details for protein glycation within the body both in terms of the nature of the chemical modifications and proteins modified. Despite this, these cardiovascular and other problems associated with diabetes are attributed to protein glycation that result in cell and tissue pathology. In fact, the gold standard for dietary glucose compliance by the patient is the measurement of glycated haemoglobin (HbA_{1c}). HbA_{1c} is formed as a function of elevated blood glucose concentration and time as a result of a lack of dietary compliance [11]. Protein glycation is a complex and poorly defined phenomenon at the molecular level [7,8] despite its profound effect on many processes including ageing and inflammation [5,12–14]. Detailed and systematic biochemical studies using structurally-defined targets such as albumin and haemoglobin have identified structural properties of proteins that facilitate glycation [15–17]. In the case of albumin glycation, this chemical process is controlled by the surrounding chemical microenvironment with the potential to generate glycation hotspots [16,17].

In this mini review we extend our hypothesis [4] by reviewing other systems; these systems provide more general support for the concept that protein glycation generates negatively charged macromolecules and that these molecules stimulate innate immunity by binding to the appropriate receptor, leading to adverse tissue responses. In particular, we highlight two systems. The first system involves the lectin-like oxidised receptor (LOX-1) as this is a well-established system involving the anionic macromolecule, electronegative LDL (LDL(–)) that can be formed as a result of protein glycation and is critically involved in CVD via binding to the LOX-1 receptor. This system is a very important example of how the generation of an anionic macromolecule results in a pathological response in tissues. The second system involves the Triggering Receptor Expressed on Myeloid cells-2 (TREM-2) and has implications for the development of dementia. A comparison of LOX-1 and TREM-2 with RAGE that we have previously mentioned with respect to COVID-19 morbidity and mortality [4], shows many functional similarities not previously compared. Therefore, we hypothesise that this anionic LDL is also a ligand for RAGE and TREM2, a concept that provides a molecular basis for many inflammatory diseases.

2. LOX-1 and CVD

An anionic derivative of LDL referred to as electronegative LDL (LDL(–)) is strongly linked to the development of atherosclerosis and associated cardiovascular disease (CVD), the major cause of death worldwide and is associated with diabetes and ageing [18–22]. This is the first clear example of how chemical modifications of a protein provides a molecular pathway for the development of a pathological condition. In fact, the modification of LDL has a long history of involvement in CVD as a result of becoming more negatively charged and no longer able to bind to the LDL receptor. Early work from the laboratory of Brown and Goldstein to investigate the role of modified LDL in CVD utilised chemical acetylation of LDL to modify lysine residues on the protein surface. The resultant loss of positive charge resulted in a negatively-charged modified LDL that changed its receptor binding characteristics. This modified LDL no longer binds to the classical LDL receptor but instead binds to the macrophage scavenger receptor (SR-B1) resulting in a massive uptake of lipid to produce foam cells characteristic of atheromatous plaques [23]. Subsequently, modified (negatively-charged) LDL that bound to SR-B1 was produced by incubating LDL in vitro with endothelial cells (ECs) [24]. The term oxidised LDL has been routinely used to describe LDL that is modified both in vivo and in vitro to become negatively charged and now binds to scavenger receptors. The precise chemical nature of oxidised LDL and LDL(–) has yet to be determined. Oxidised LDL has been detected in vivo using immunological methods while preparation of oxidised LDL in vitro uses copper-induced oxidation. LDL(–) is detected in samples of LDL using anion-exchange

chromatography and accounts for 4 % (ranging from 0.5 to 9.8 %) of all LDL [25]. Oxidised LDL and LDL(–) have been critically discussed in a recent review [25]. We will specifically discuss LDL(–) but will use the term anionic LDL where necessary to cover both these modified proteins.

Growing evidence suggests that a number of modifications can elicit atherogenic properties in LDL. These modifications may include glycation, desialylation, carbamylation or enzyme induced lipolysis or proteolysis [19]. A characteristic that describes most of these modifications is an increase in negative charge of the LDL particle [19]. In particular, glycation has been proposed as one event that produces LDL(–) [19,26] and is associated with diabetes and hyperglycaemia. However, there is little molecular detail available about LDL glycation. The binding of LDL to the LDL receptor involves cationic residues on the LDL binding to anionic residues on the LDL receptor [27]. Therefore, since glycated LDL does not bind to the LDL receptor, one possibility is that these cationic residues are a target for glycation.

LDL(–), like the original acetylated LDL or oxidised LDL, is not recognised by the normal LDL receptor but signals, in particular, via LOX-1 [20–22,28]. The importance of LOX-1 in CVD has been highlighted as it plays a major role in modified LDL metabolism and CVD [20–22,29,30]. It was first described as a membrane receptor for oxidised LDL in endothelial cells (ECs) [31,32] and has since been shown to be expressed in other cell types including cardiomyocytes, fibroblasts, lymphocytes, macrophages, dendritic cells and neutrophils [20,21]. LOX-1 binds modified LDL within its extracellular lectin-like domain which has a basic backbone of arginine residues that preferentially binds to negatively charged molecules [33] including LDL(–). In ECs, ligand binding stimulates signal transduction via several signalling pathways to change the cellular phenotype from anti-inflammatory to pro-inflammatory which, in pathological conditions, results in endothelial dysfunction leading to atherosclerosis and CVD. Expression of LOX-1 is an example of regulation involving positive feedback. Within the promoter region there are recognition sequences for both nuclear factor kappa B (NFκB) and activator protein 1 (AP1). A positive feedback loop is initiated in which binding of the modified LDL to LOX-1 stimulates NFκB and AP1 resulting in further LOX-1 expression [20,21,34]. Thus, a positive feedback loop will produce a rapid and dramatic response on anionic ligand binding. The modification of LDL and its subsequent involvement in CVD is summarised in Fig. 1.

3. TREM2 and dementia

The stimulation of innate immunity (basal or low-grade inflammation) involves other receptors for anionic molecules that can lead to different disease processes. Our second example to be discussed in this review is TREM2, which is expressed in microglia (the macrophages of the brain) among other cells, and is linked to neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease and prion diseases [35–38]. A key feature of these diseases is the accumulation of amyloid-β however the molecular mechanisms underlying this accumulation are still poorly understood. It is possible that there is a direct molecular link between protein glycation and the formation of amyloid and this has been critically reviewed [39]. Alternatively, the interaction of glycated anionic macromolecules with TREM2 could adversely affect amyloid-β processing and this is discussed below.

TREM2 is another transmembrane receptor capable of binding multiple anionic ligands including phosphatidylserine [40] associated with innate immunity [35]. It has a pronounced basic (cationic) patch on its surface that allows it to bind to these ligands [35]. An important role for TREM2 in amyloid – β pathology and plaque processing (amyloidosis) by microglia is central to our understanding of dementia [36]; it is reported that TREM2 is a receptor for amyloid β [41]. In fact, TREM2 is now a major focus in understanding the accumulation of amyloid β in the nervous system [35–38]. A complex relationship exists between TREM2 and Apolipoprotein E (ApoE), the genetic risk factor most strongly linked to AD, [36] with evidence that TREM2 is an ApoE

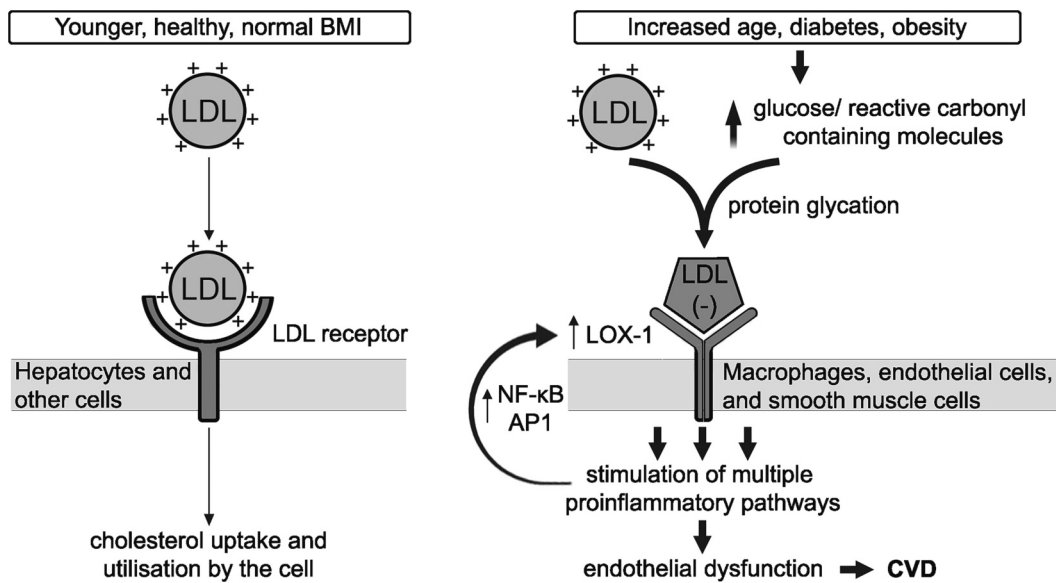


Fig. 1. Proposed role of LDL glycation in driving cardiovascular disease in ageing, diabetic and/or obese patients. In a younger healthy person with a normal BMI, LDL is taken up by cells of the body, particularly hepatocytes, via the LDL receptor to provide the cell with the cholesterol it requires for normal function. In the case of hepatocytes, large amounts of cholesterol are required for bile acid synthesis. Increasing age, compounded by obesity and hyperglycaemia as seen in Type II diabetes will promote protein glycation and other chemical modifications to produce negatively-charged LDL (oxidised LDL). This modified protein no longer binds to the LDL receptor but binds to the innate immunity receptor, LOX-1, via electrostatic interactions, stimulating multiple pathways leading to CVD.

receptor [42,43]. Clearly, there is a complex pattern of interaction involving anionic ligands that will affect microglial function and amyloid processing. The binding of inappropriate anionic ligands to TREM2 as a result of protein glycation would lead to adverse effects on microglia function and amyloid accumulation. This altered function may be crucial in the development of dementia, particularly in the later stages of the disease [36] (Fig. 2). The concept of anionic structures binding to TREM2 and affecting its function may have other ramifications. In particular, a possible link between traumatic brain injury (TBI) and dementia has been widely discussed. Tissue damage within the brain would result in the release of anionic ligands leading to sterile inflammation [9] and the binding of such ligands to TREM2. Such a response may adversely affect the functioning of TREM2 and amyloid processing leading to dementia as a result of anionic ligands interacting with TREM2 (Fig. 2).

4. RAGE, LOX-1 and TREM2

These two examples of innate immunity have remarkable parallels with the RAGE system [4-6] and the generation of a basal or low-grade inflammatory state. All three receptors have a cationic domain and can bind non-specifically via non-specific electrostatic interactions to anion surfaces presented as invading micro-organisms or damaged tissue. All three will bind to membranes rich in phosphatidylserine that are characteristic of apoptotic cells. In the case of RAGE and LOX-1, both receptors show a characteristic of positive feedback regulation of gene expression, an unusual characteristic for biological systems. A positive feedback loop has yet to be confirmed for TREM2 expression. A positive feedback loop in innate immunity may reflect the need of the body to respond rapidly and dramatically to an infection or significant tissue damage before the body is overwhelmed by the insult. Such systems have the potential to produce adverse pathological situations. It should

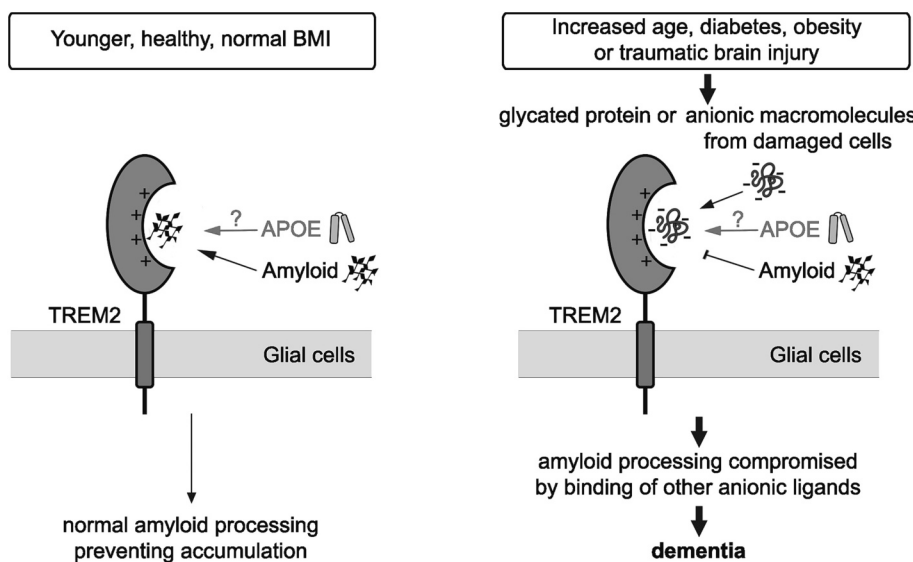


Fig. 2. Proposed role of glycosylated proteins and/or anionic macromolecules arising from ageing, diabetes, obesity or traumatic brain injury in dementia as a result of interaction with TREM2. In a younger healthy person with a normal BMI the receptor on glial cells, TREM2 is a typical innate immunity receptor that is proposed to be involved in amyloid processing and may prevent amyloid accumulation and dementia. We hypothesise that anionic macromolecules that can arise from protein glycation or as a result of the release of cell debris due to traumatic brain injury can bind to TREM2. This binding may adversely affect amyloid processing in the later stages of dementia [36]. We hypothesise that electronegative (oxidised) LDL acts as an anionic ligand for TREM2 and adversely affects TREM2 function (Fig. 3).

be emphasised that each receptor may generate its own unique pathology as a result of location, RAGE in lung epithelial cells, LOX-1 in endothelial cells of the CV system and TREM2 in microglial cells of the brain.

RAGE, LOX-1 and TREM 2 share a further characteristic, the extra-cellular region of the receptor can be cleaved by a disintegrin and metalloprotease (ADAM), in particular ADAM10, to generate sRAGE [44] sLOX-1 [45] and sTREM2 [46] respectively. In all cases the soluble form of the receptor is still able to bind anionic ligands but the precise physiological role(s) of these soluble receptors remains to be determined but could be linked to the down regulation of the receptor. They are useful biomarkers for assessing levels of the cell-associated receptor.

The similarities of these receptors raise the possibility that anionic LDL could also be a ligand for TREM2 and RAGE. Anionic LDL is possibly the only established example of an abundant extra-cellular protein that changes its charge as a result of protein modification. Moreover, the high concentration of LDL in the circulating serum protein would mean that chemical modification by protein glycation and other mechanisms would result in significant concentrations of LDL (-) being generated, 0.5 to 9.8 % of total LDL [25]. Both TREM2 and RAGE receptors bind anionic ligands in a non-specific manner while electronegative LDL is already clearly established as having a central role in disease processes. We suggest that such an interaction could exacerbate the lung

inflammation and dementia that is associated with age, obesity and hyperglycaemia (Fig. 3).

At this time there appears to be only one report that electronegative LDL may be a ligand for RAGE [47] while glycated LDL has been included as a RAGE ligand [8]. There appears to be no published report of anionic LDL being a ligand for TREM2 although it might be anticipated [35] as this modified LDL is both anionic and lipid in nature. It should be noted that oxidised phosphatidylcholine (PC), a possible covalent modification in LDL(-) based on antibody detection [25] is cleared by TREM2 [48]. If anionic LDL is to bind to TREM2 it must first be able to pass through the blood brain barrier. Evidence to support this is sparse but supportive [49,50] while the link between cardiovascular disease and dementia is well established with a considerable literature.

5. Conclusion and future perspectives

In summary, in this review we highlight the importance of protein glycation; resulting in the formation of anionic macromolecules such as anionic LDL that are perceived by the innate immune system as foreign or arising from damaged tissue. An inflammatory response ensues as a result of the binding of the anionic protein to the appropriate scavenger receptor. The seminal observation from the Brown and Goldstein laboratory on the chemical acetylation of LDL in 1979 [23] is a paradigm for how the chemical (non-enzymatic) generation of negative charge on proteins can drastically affect their biological properties. Here we discuss the glycation of LDL resulting in the formation of the anionic LDL (LDL(-) or oxidised LDL) a protein that is bound to LOX-1 of ECs as well as macrophages and vascular smooth muscle cells, initiating molecular processes that lead to CVD. The LOX-1 system provides a clear molecular pathway from glycated protein, anionic LDL, via stimulation of the LOX-1 receptor to CVD. In contrast, the molecular pathway involving protein glycation that leads to dementia is unclear. However, we suggest that such anionic proteins (anionic LDL) could bind to TREM2 in microglia of the brain and interfere with amyloid- β processing resulting in amyloid- β accumulation. Similarly, anionic LDL could bind to RAGE and exacerbate lung inflammation, as previously discussed in general terms [4]. Thus, the inflammation promoted by the glycated (anionic) protein will depend on both the nature of the protein and the location of the scavenger receptor. It must be appreciated that protein glycation is only one of a number of chemical modifications that affect proteins, while their attached ligands will change the surface charge on the particle [25]. It is important to note that while LOX-1 is an established receptor involved in LDL uptake and atherosclerosis, the role of RAGE and TREM2 in LDL binding is less studied. Consequently, biophysical studies providing information regarding binding sites, binding affinities of anionic LDL with RAGE and other endogenous ligands is limited. Future work will require detailed biophysical studies of anionic LDL binding to both TREM2 and RAGE to confirm that anionic LDL is a physiologically relevant ligand for these two scavenger receptors.

In conclusion, this review further highlights the importance of a healthy diet avoiding excessive intake of sugar to prevent prolonged hyperglycaemia and obesity and the resulting protein glycation by glucose and carbonyl-containing metabolites [7,8]. It must be stressed though that the chemically reactive carbonyl group of glucose and other biochemicals is essential for the functioning of metabolic pathways such as glycolysis within the cell. The problem is having too high a concentration of these carbonyl-containing compounds within the body for too long. Inherent in this concept is the development of a basal or low-grade inflammatory state within the body. This basal or low-grade inflammatory state may have profound consequences for the development of many diseases linked to ageing, obesity and hyperglycaemia including pathological COVID-19, CVD and dementia.

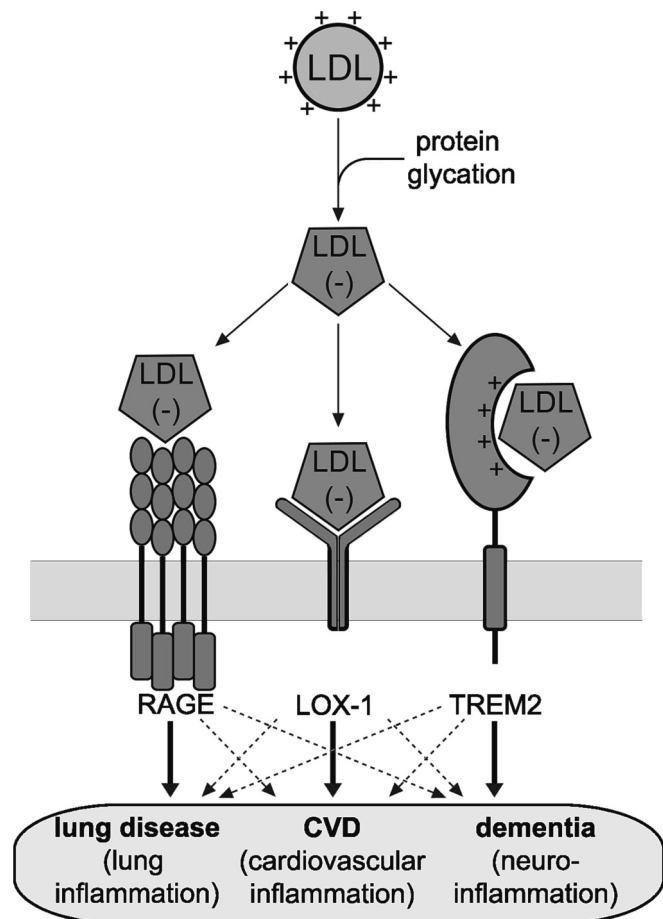


Fig. 3. Proposed role of oxidised LDL in lung disease, CVD and dementia. We hypothesise that electronegative (oxidised) LDL may also be the common ligand in exacerbating lung disease via RAGE and dementia via TREM2 as well as being central to CVD. This hypothesis would fit with factors such as age, obesity and hyperglycaemia that are linked to these three pathological conditions. It is possible that each receptor, on binding this modified LDL, can adversely affect other tissues as these receptors have a wider distribution in body tissues [5,20,35].

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Declaration of competing interest

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Data availability

No data was used for the research described in the article.

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