

# A Proteome-Centric View of Ageing, including that of the Skin and Age-Related Diseases: Considerations of a Common Cause and Common Preventative and Curative Interventions

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**Abstract:** The proteome comprises all proteins of a cell or organism. To carry their catalytic and structure-related functions, proteins must be correctly folded into their unique native three-dimensional structures. Common oxidative protein damage affects their functionality by impairing their catalytic and interactive specificities. Oxidative damage occurs preferentially to misfolded proteins and fixes the misfolded state. This review provides an overview of the mechanism and consequences of oxidative proteome damage – specifically irreversible protein carbonylation – in relation to ageing, including that of the skin as well as to age-related degeneration and diseases (ARDD) and their mitigation. A literature review of published manuscripts, available from PubMed, focusing on proteome, proteostasis, proteotoxicity, protein carbonylation, related inflammatory diseases, ARDD and the impact of the damaged proteome on ageing. During ageing, proteome damage, especially protein carbonylation, correlates with biological age. Carbonylated proteins form aggregates which can be considered as markers and accelerators of ageing and are common markers of most ARDD. Protein carbonylation leads to general ageing of the organism and organs including the skin and potentially to diseases including Alzheimer and Parkinson disease, diabetes, psoriasis, and skin cancer. Current research is promising and may open new therapeutic approaches and perspectives by targeting proteome protection as an age and ARDD management strategy.

**Keywords:** proteome, protein folding, oxidative stress, protein carbonylation, skin ageing, antioxidant chemical chaperones

## Introduction

Proteome comprises the ensemble of proteins in any organism.<sup>1</sup> The term proteome was presented for the first time in 1994. Since then, proteomic research has become a key area of cellular biology leading to the identification of numerous post-translational modifications (PTM), both physiological and non-physiological, such as toxic redox-dependent modifications – called oxidative damage – identification of oxidative stress factors and potential therapeutic solutions.<sup>2</sup> Research is still ongoing and provides new information about the role of the healthy or damaged/stressed proteome.

Proteins are the most diverse and structurally complex macromolecules in the cell. They participate in nearly every known aspect of life, either directly or by synthesizing other active biomolecules. Their function is determined by the specific native three-dimensional structures which are perturbed either by mutations or direct chemical damage. While the effects of mutations have been studied since the beginnings of molecular genetics and biology, protein damage, unlike DNA damage, was largely neglected (used as a mere biomarker of cellular oxidative damage) until the early nineties and more recently investigated by our group. These specific native three-dimensional structures ensure that new polypeptide chains adopt, and native proteins keep their properly folded conformation, even during stressful situations.<sup>3</sup>

The concept that protein carbonylation determines ageing and age-related degeneration and diseases (ARDD) was promoted in 2016 by quantifying the capacity of individual *E. coli* cells infected after irradiation to produce phase

particles.<sup>4</sup> According to the author, the first issue in cell recovery from radiation damage is related to the proteome rather than DNA, since prokaryotic and eukaryotic cell death correlates with incurred protein, but not DNA, damage by reactive oxygen species (ROS).<sup>5</sup> Therefore, proteome protection against oxidative damage determines survival after ionizing or UV irradiation, since sufficient residual proteome activity is required to turn on the DNA damage response which activates DNA repair and protein renewal processes.<sup>6</sup> The observation that oxidative damage targeted selectively to cellular proteins results in ageing-like phenotypes suggests that ageing and ARDD could be phenotypic consequences of proteome damage patterns progressing with age.<sup>7</sup>

Protein damage was suggested to be the main issue in ARDD.<sup>2</sup> An initially silent protein polymorphism becomes phenotypic triggering ARDD through protein damaging, resulting in unrepaired DNA and thus in DNA damage and potential genetic mutations. This led the authors to propose a vision of predictive diagnosis, prognosis, prevention, and treatment of degenerative diseases, targeting proteome protection rather than conventional DNA centric approaches.

Oxidative stress caused by oxidative metabolism and environmental factors appears as the main source of proteome damage. Since proteome is the carrier of biological functions, its damage has immediate phenotypic and genetic consequences related to ageing and ARDD.<sup>2</sup>

The following work provides a comprehensive overview of what is known about proteostasis and proteotoxicity, protein damage and carbonylation, ARDD including cutaneous conditions, with a special focus on skin ageing as well as therapeutic perspectives.

To do so, we conducted a literature review of 52 manuscripts published and available from PubMed, focusing on the following key terms used alone or combined with each other: proteome, proteostasis, proteotoxicity, protein carbonylation, related inflammatory diseases, ARDD and the impact of damaged proteome on ageing.

## Healthy versus Pathogenic and Toxic Proteomes: The Role of Oxidative Damage

A healthy proteome is achieved and maintained by proteostasis – optimal turn-over of proteins, high ribosomal fidelity in translation and high accuracy of protein folding assisted by chaperone proteins (CP). This process is also called protein quality control (PQC) via the proteostasis network (PN).<sup>8,9</sup> Failing of PQC results in a low-quality proteome that misfunctions or leads to detrimental accumulation of misfolded proteins that form toxic small aggregates (oligomers) and large amyloids or fibrils.<sup>10</sup> It has been shown that protein oxidation precedes aggregation, to the extent that over 90% of carbonylated proteins are found in aggregates in bacteria and mice.<sup>11</sup> This is explained by high sensitivity to oxidation of misfolding proteins, resulting in a misfolded state that is irreversibly fixed by carbonylation.<sup>2</sup> Thus, the antioxidant defence of reversibly misfolded proteins becomes a cellular priority that allows chaperones to refold proteins before they undergo oxidative damage. Over the past years, research has shown that not all members of the PN are similarly skilled to protect the proteome against environmental and intrinsic factors that organisms might be confronted during their lifespan and are not equal in terms of sensitivity to oxidative stress.<sup>12</sup>

Over the past two decades significant research has been dedicated to more thoroughly understand how organisms protect their proteome against irreversible damage during oxidative stress associated with extreme environmental conditions such as radiation or high temperatures. Three strategies stand out: protection of proteins by neutralizing ROS and increased fidelity of protein biosynthesis and the activity of CP.<sup>13</sup> The latter have specific modes of substrate recognition that define their substrate range and specificity.<sup>14</sup> They are the heart of PN and participate in the protein folding process, support their assembly and disassembly, regulate their handling and signalling, and prevent unfolding proteins from irreversible aggregation.<sup>13</sup> CP are assisted by co-chaperones which adjust the action of chaperones, and collaborate with catalytic folding factors, proteases and non-proteinaceous chaperones.<sup>15</sup> CP interact without being part of the latter.<sup>8</sup>

## Protein Carbonylation and Proteotoxicity

Oxidative stress is the imbalance between pro- and antioxidants in favour of the former, hence causing proteotoxicity.<sup>16</sup> Proteotoxicity is cellular dysfunction, caused by protein misfolding, damage and aggregation. It is used as a biomarker of a number of ARDD, including diabetes and cancer.<sup>17,18</sup> Environmental aggressions, such as radiations, can trigger

overproduction of ROS or the impairment of the antioxidant defences.<sup>19</sup> An increase in intracellular ROS results in oxidative stress and important irreversible protein damage (carbonylation) that fixes the misfolded protein structure, leading to protein aggregation, impossible to eliminate via autophagia or proteasome and thus ultimately to cell death.<sup>20</sup>

Protein carbonylation is the irreversible post-translational modification (PTM) of proteins that affects the exposed side chains in proteins in the form of an aldehyde, ketone, or lactam group.<sup>21</sup> Protein carbonylation is the most frequent oxidative damage affecting proteins.<sup>22</sup>

Proteotoxicity of protein carbonylation is a determinant of cellular sensitivity to desiccation and irradiation, also involved in the progression of ARDD, including neurodegeneration and cancer.<sup>23</sup>

## Protein Carbonylation and ARDD

Oxidative modifications of enzymes and structural proteins are involved in the aetiology and/or progression of several human diseases and ageing processes. Therefore, permanent surveillance by CP ensures proteostasis. As a result of age-related dysfunction in proteostasis, protein-aggregation diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD) may develop.

Protein aggregate deposits in fibrillar and amyloid-like forms indeed appear as characteristics of a certain number of neurodegenerative diseases such as AD, PD and other ARDD.<sup>18,24</sup>

During the natural process of ageing, PN is increasingly impacted by a growing load of misfolded and damaged proteins, especially in neurons.<sup>25</sup> Therefore, the age-dependent deterioration of the capacity of cells to maintain a functional proteome is considered as a main cause of ARDD.<sup>26</sup> Moreover, it has been reported that in the human brain, ATP-dependent chaperones become inhibited during the ageing process, thus increasing the risk of protein misfolding, oxidation and aggregation.<sup>27</sup>

Both AD and PD share several common pathological features, comprising the accumulation of protein aggregates linked with defects in autophagy, preventing the maintenance of neuronal proteostasis.<sup>28</sup>

In diabetes, both insulin deficiency and insulin resistance are linked to inefficient mitochondrial coupling and excessive production of ROS, resulting in proteome damage and degradation.<sup>18,29</sup> As in AD and PD, diabetes 2 displays oligomerisation and the aggregation of a specific protein (IAPP or amylin).

## Proteome Damage and Human Skin

In the aetiology of different skin conditions and diseases, skin ageing, psoriasis, and, potentially, atopic dermatitis and skin cancers, including melanoma as well as squamous and basal cell carcinoma have been related to protein damage.<sup>30,31</sup> With skin cancer mechanisms involving not only proteins but also DNA damage, the repair of which is reduced in proportion to protein damage. This review does not further expand on DNA damage.

## Skin Ageing

The skin protects the body from environmental physical and biological aggressions. It is directly exposed to environmental aggressions and stimuli, such as UV radiation, humidity, temperature, xenobiotics (viruses, bacteria, fungi, and parasites) and chemical pollutants.<sup>12</sup> UV, UVA, UVB and UVC light are considered as one of the main causes of excessive ROS production and protein carbonylation in the skin.<sup>32</sup>

Increased protein carbonylation in the skin is associated with a negative impact on complexion, hydration and dermal structure, thereby accelerating skin ageing; it is considered a hallmark of oxidative stress of the skin.<sup>33</sup> In the dermis, accumulation of carbonylated proteins in fibroblasts has been shown to increase protein aggregation and morphological changes at the cellular level. Comparable to neuronal cells, dermal fibroblasts are long-lasting cells undergoing damage accumulation, as a skin ageing biomarker.<sup>34,35</sup>

In an *in vitro* assay, Wang et al demonstrated that UVA significantly triggers the breakdown of collagen fibres in the dermis, fibroblast apoptosis and DNA damage, while UVB triggers protein carbonylation and keratinocyte proliferation.<sup>36</sup>

Several molecular mechanisms, including oxidative stress, mitochondrial DNA mutations, DNA damage, telomere shortening, hormonal changes, and autophagy impairment, have all been listed for their involvement in skin ageing.<sup>37</sup> Most of these mechanisms relate to proteotoxicity or proteome damage.

## Psoriasis and Atopic Dermatitis

The extracellular matrix (ECM) is known for supporting the skin and to direct its cell functions. A disturbed ECM may cause various skin diseases.<sup>38</sup> Among these, psoriasis and atopic dermatitis are frequently reported.<sup>12,39</sup>

While the pathogenesis of psoriasis is still unclear, the role of damaged proteins is increasingly proposed.<sup>40</sup> Inflammation that occurs in psoriasis is associated with skin cells (keratinocytes and fibroblasts) and immunity (both innate and adaptive). Tumour necrosis factor (TNF $\alpha$ ) has been implicated in the pathogenesis of psoriasis. It triggers ROS production in primary human keratinocytes, which then, in turn, leads to the induction of cytokines, inflammation and protein carbonylation.<sup>41</sup>

Reindl et al evaluated the plasma proteome profiles of patients with psoriasis and healthy individuals.<sup>42</sup> Among 208 proteins with significantly altered levels in psoriatic plasma, changes in levels of desmoplakin, complement C3, polymeric immunoglobulin receptor, and cytokeratin 17 correlated well with PASI (Psoriasis Area Severity Index). Thus, increased levels of carbonylated or otherwise damaged plasma proteins might signal a link between proteome damage and disease.

In 2020, Karabowicz et al investigated the relationship between the intensity of oxidative stress and the expression and activity of the proteasomal system, as well as autophagy, considered as responsible for increased levels of protein carbonylation in the blood cells of patients with psoriasis. The authors showed that the decreased activity of the 20S proteasome, along with increased autophagy and protein carbonyls and of 4-HNE-protein adducts, shows an imbalanced proteome in blood cells of patients with psoriasis.<sup>41</sup>

As in psoriasis, protein carbonylation may play a significant role in atopic dermatitis.<sup>43</sup>

## Therapeutic Perspectives

In 2020, a reliable method for the measurement of human plasma protein carbonylation, which can be used for the assessment of carbonylome age-related biomarkers, was described for the first time.<sup>44</sup>

Typical defence mechanisms against high ROS burden are detoxifying enzymes, such as superoxide dismutases, catalase, peroxiredoxins, glutathione peroxidases, as well as non-enzymatic components, such as L-ascorbate,  $\alpha$ -tocopherol,  $\beta$ -carotene, uric acid, CoQ10, and the whole glutathione system. The skin is well equipped with several of these enzymes, including enzymatic and non-enzymatic antioxidants. Of those,  $\alpha$ -tocopherol and  $\beta$ -carotene applied topically were shown to be effective in some studies.<sup>34,45</sup>

A further possibility may be to render proteins, rather than genes, the target of disease management, by protecting the proteome from deleterious oxidative damage using small chemical chaperone-like antioxidants.<sup>46</sup> Mini-chaperones and desagregases act to eliminate large protein aggregates, block amyloid fibril formation, and stabilize mutant proteins. They could also be effective in preventing the protein disorder cascade.<sup>47</sup>

Different therapeutic perspectives were proposed: vitamins that protect from oxidative stress, aryl hydrocarbon receptor (AHR) that activate innate immunity, aquaporin 3 (AQP3) that reduces senescence in skin fibroblasts by promoting autophagy, natural antioxidants that have redox-balancing and/or iron-chelating properties or peptides that have notable effects on chronologically aged and/or photo-damaged skin.<sup>48–50</sup> Moreover, senolytics or compounds that neutralize SASP (senescence-associated secretory phenotype) by killing the senescent cells as well as flavonoids that reduce or prevent the ageing-associated decline by targeting senescent cells or SASP and caloric restriction and physical exercise that support proteostasis by stimulating and balancing the production and reprocessing of intracellular proteins have been suggested.<sup>51,52</sup> Unfortunately, none of these approaches has yet demonstrated thorough clinical efficacy in preventing or mitigating ARDD or skin ageing.

Thus, a therapeutic approach that acts at the root cause of all ARDD and ageing phenotypes including that of the skin could be beneficial. Synthetic or natural molecules which display chaperone-like antioxidant activity and protect the

proteome against protein carbonylation, aggregation and degradation induced by diverse stresses involving ROS may be another interesting novel approach to preserve proteostasis.

A bacterial extract from *Arthrobacter agilis* that displays chaperone-like antioxidant activity and protects the skin proteome against carbonylation may thus become a new actor in the protection of the proteome and can, in the field of dermatology, protect the skin against “exposome”, especially UV radiations that lead to premature ageing of the skin.<sup>19</sup>

## Discussion

Protein damage appears as a common cause of ageing and ARDD. While most proteins have been selected for their resistance to oxidative damage, any folding imperfections appear to reduce their resistance to oxidation. Such damaged proteins accumulate with age and trigger ageing-like phenotypes. While natural protein turnover allows reversibility to a certain extent, acquired alterations (genetic and epigenetic) of the genome result in permanent protein malfunction or deficit.

For decades, biomedical research has focused on ARDD as opposed to the ageing process itself and much of this research has centred on studying and treating consequences rather than causes. There are many mechanisms for protecting, repairing, and maintaining cells, but ageing still occurs with species-specific speed. Thus, the key to limit ageing may come from protection against incurring damage, in particular protein damage.

In the skin ageing process, oxidative stress of the proteome plays a major role. Intrinsic ageing of the skin is caused by metabolism and genetic factors, but environmental factors seem to dominate skin ageing. Although results are quite different in the dermis and epidermis, extrinsic ageing is driven to a large extent by oxidative stress caused by UV radiations.<sup>32</sup>

Among various approaches, molecules that display chaperone-like antioxidant activities and protect the skin proteome against carbonylation may become new actors in the protection of the proteome and can, in the field of dermatology, protect the skin against “exposome”, especially UV radiations that lead to premature ageing of the skin.<sup>19</sup>

Much research remains to be done to confirm this new preventative and therapeutic concept, not only in skin ageing but also in inflammatory skin diseases such as AD and psoriasis, and potentially in cancer, because cancers display high protein carbonylation and increased chaperone levels (diagnostic of misfolded proteins). Thus, CP-like antioxidants may open new perspectives for the management of ARDD. Although much investigation remains ahead, it seems as is defence against proteome damage may be a target to protect the organism against the biological effects of environmental stress and age.

## Data Sharing Statement

The data that support the findings of this work are available from Isabelle Benoit, the corresponding author upon reasonable request.

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