


Review

Oxidatively Modified Proteins: Cause and Control of Diseases

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Abstract: Proteins succumb to numerous post-translational modifications (PTMs). These relate to enzymatic or non-enzymatic reactions taking place in either the intracellular or extracellular compartment. While intracellular oxidative changes are mainly due to redox stress, extracellular PTMs may be induced in an inflammatory micro milieu that is rich in reactive species. The increasing recognition of oxidative modifications as a causing agent or side-effect of pathophysiological states and diseases puts oxidative PTMs (oxPTMs) into the spotlight of inflammation research. Pathological hyper-modification of proteins can lead to accumulation, aggregation, cell stress, altered antigenic peptides, and damage-associated molecular pattern (DAMP)-like recognition by host immunity. Such processes are linked to cardiovascular disease and autoinflammation. At the same time, a detailed understanding of the mechanisms governing inflammatory responses to oxPTMs may capitalize on new therapeutic routes for enhancing adaptive immune responses as needed, for instance, in oncology. We here summarize some of the latest developments of oxPTMs in disease diagnosis and therapy. Potential target proteins and upcoming technologies, such as gas plasmas, are outlined for future research that may aid in identifying the molecular basis of immunogenic vs. tolerogenic oxPTMs.

Keywords: immunogenicity; MHC; post-translational modifications

1. Introduction

Proteins are targets for immune cells, and modifications like aggregation are known to link to the pathogenesis of several diseases [1,2]. However, the cause of this protein aggregation is not always clear. Increasing evidence points to the relevance of post-translational modifications (PTMs) caused by not only enzymatic PTMs but also reactive oxygen and nitrogen species (here abbreviated as ROS, as RNS also include oxygen) [3,4]. Under physiological conditions, ROS are essential regulators for maintaining homeostasis and serve as signaling molecules [5]. Interestingly, cells of the innate immune system are major contributors to the inflammation and ROS production in such conditions [6,7]. Excessive inflammation leads to overshooting ROS production, which is often associated with autoimmunity and carcinogenesis [8,9]. The immune system is a double-edged sword in these two processes: In chronic inflammation and autoimmunity, cells of the adaptive immune system are major contributors to self-antigen-related tissue destruction and the production of autoantibodies targeted against the host [10,11]. Nonetheless, T cells directed against oncofetal or aberrant host proteins are a desired event in oncology and pertained in the clinic using checkpoint therapy to augment anti-tumor immunity [12,13]. Checkpoint therapy and other modulating immune effectors address such diseases, as they develop not only through the proteins and their PTMs but also because of the interaction between proteins and cells of the immune system.

Immune cells recognize structures on the cell surface to decide if a cell is healthy or not. The latter leads to immune cell activation and elimination of the infected, cancerogenic, or foreign

cell. Not naturally occurring PTMs can mimic a non-self-structure and trigger an immune response, which can have advantages and disadvantages. On the one hand, this leads to an unwanted killing, as evident in neurodegenerative or autoimmune diseases. On the other hand, PTMs are promising as biomarkers for diagnosis and are increasingly recognized as novel agents for the treatment of cancer and allergies.

In this review, we describe various protein modifications that are linked to diseases: (I) the consequence of enzymatically driven changes, (II) the origin of non-enzymatic-induced PTMs and related disorders, (III) the immunogenicity of PTM-bearing epitopes, and (IV) the putative therapeutic use of PTMs. Finally, we outline novel tools for oxidative PTM research that not only rely on the generation of one kind of reactive species but a multitude of reactive species simultaneously, which aids in mimicking the inflammatory environment.

2. Overview of Enzymatic Post-Translational Modifications

Enzymatic PTMs, such as phosphorylation, acetylation, glycosylation, and ubiquitination, regulate protein function and interaction [14–16]. Enzymes (kinases, transferases) catalyze the covalent modification of an amino acid side chain and sometimes require co-substrates (e.g., ATP). While some enzymatic PTMs lead to activation or inhibition of intracellular proteins and are critical events in signal transduction [17–21], other enzymatic PTMs are essential for protein stability and regulation. For instance, the tumor suppressor p53 is stabilized by phosphorylation and regulated by an array of PTMs in more than 36 different amino acids [22–24]. Enzymatic PTMs transform the p53 protein folding, stability, and function. Although defective regulation leads to misfolding and malfunction of the protein, incorrect folding of p53 alone does not necessarily lead to cell cycle defects and tumor growth. Still, enzymatic PTMs are causative in the dysregulation of kinases, malfunction or misfolding of proteins, and aggregation of proteins that ultimately can cause diseases.

In Alzheimer's disease (AD), aberrant enzymatic activity promotes hyperphosphorylation of the tubulin-associated unit (tau) protein leading to its oligomerization and aggregation [25]. However, aggregation of amyloid- β is a commonly assumed primary pathological process, as the amyloid hypothesis states that this aggregate promotes tau modification [26,27]. Amyloid- β aggregates enable redox-active metal ions to bind, which catalyzes the production of ROS [28]. The increased amount of intracellular ROS is then self-amplified via mitochondria. Hence, ROS and their subsequent non-enzymatic modifications on proteins causing, for instance, oxidation, chlorination, or nitration are intertwined with enzymatic PTMs processes.

3. Redox Stress and oxPTMs as the Cause of Different Diseases

Intracellular compartments, such as mitochondria, peroxisome, and endoplasmic reticulum, generate endogenous ROS. ROS can be classified in independently existing heavy reactive radicals and non-radical species. Radical species include superoxide ($O_2^{\circ -}$), oxygen radicals ($O_2^{\circ \circ}$), hydroxyl (OH°), alkoxy radical (RO°), peroxy radical (ROO°), nitric oxide (NO°), and nitrogen dioxide (NO_2°). Examples for non-radicals include hydrogen peroxide (H_2O_2), hypochlorous acid (HOCl), hypobromous acid (HOBr), ozone (O_3), singlet oxygen (1O_2), and peroxynitrite (ONOOH). ROS interact with intracellularly present proteins and induce modifications resulting in altered protein activity and function [29]. Although a balance of ROS level is sustained via enzymes and antioxidants, increased concentration of ROS is sometimes inevitable and leads to oxidative stress. Several diseases link to redox stress and ROS due to an unbalanced ROS homeostasis, such as diabetes, atherosclerosis, neurodegenerative diseases, macular degeneration, cancer, and others [30–33]. As a consequence, significant differences in enzyme activity lead to increased oxidative damage and lipid peroxidation [34–37]. Since many diseases can arise from redox stress, they show a specific fingerprint. Therefore, biomarkers of oxidative stress become increasingly relevant in the diagnosis of neurodegenerative diseases [38]. Oxidative stress, but also hypoxia, inflammation, and mutations in particular proteins, are just a few of the causes that lead to unfolded protein response

(UPR). For example, tumor necrosis factor receptor-associated periodic syndrome is caused by UPR, and enhanced production of ROS in monocytes was determined in patients [39,40], suggesting a role for ROS-induced PTMs. For UPR, a somewhat more complex, but not negligible, correlation is shown between proteins and diseases [41–44]. UPR and redox stress are not only present in AD, atherosclerosis, diabetes, and inflammatory diseases, but also in asthma [45,46]. Evidence shows an increased amount of redox stress inhibitor hypoxia-inducible factor-1 during the development of allergic airway inflammation, and modulation of ROS improves the hyperresponsiveness suggesting ROS as a cause for asthma [47,48]. Since ROS can be scavenged and dampened by antioxidants, a number of therapies based on antioxidants have been postulated.

In analogy to the phosphorylation system, oxidases and reductases regulate thiol groups on proteins for their activation or inactivation as signaling molecules, or transcription factors [5,49]. To control redox-signaling transmission, homeostasis of intracellular ROS levels requires enzymes and other antioxidant proteins [50–52]. The most important enzymes for ROS homeostasis are nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, xanthine oxidase, superoxide dismutase (SOD), nitric oxide synthase (NOS), NADPH oxidase (NOX), and myeloperoxidase (MPO) (Figure 1). An imbalance of the mentioned enzymes and their activity can lead to diseases.

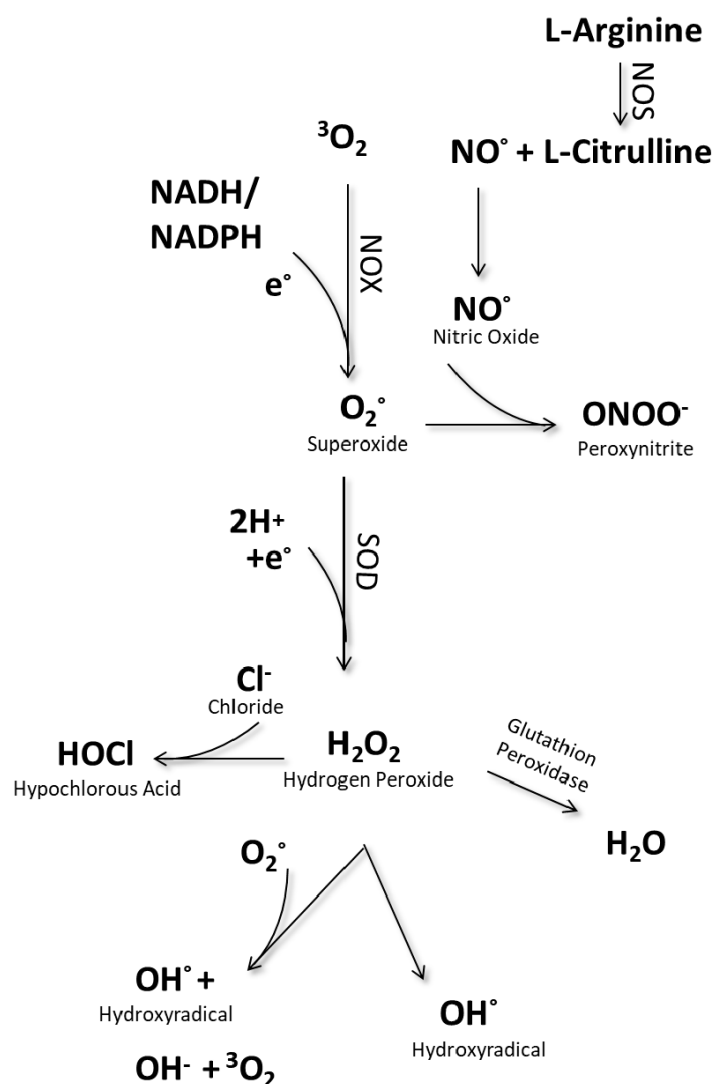


Figure 1. Intracellular generation of reactive species.

For instance, SOD catalyzes the dismutation of radical superoxide anion (O_2^-) into hydrogen peroxide (H_2O_2) or ordinary molecular oxygen (O_2). Dysregulation of SOD and total antioxidant capacity leads to oxidative stress and chronic hyperglycemia, as evident in diabetic disease [53–55]. Altered SOD levels, oxidative stress, and cytoplasmic aggregates have also been shown in amyotrophic lateral sclerosis [56,57]. Another relevant protein, myeloperoxidase (MPO), catalyzes the oxidation of chloride ion and converts thiocyanate to generate isocyanic acid. Isocyanic acid induces immunogenic PTMs as α -carbamylation and homocitrulline (ϵ -carbamyl-lysine) [58]. Carbamylated proteins accumulate in tissues and are mostly associated with aging [59,60], while citrullinated proteins are related to autoimmune diseases, such as rheumatoid arthritis (RA) (Table 1). The example of RA illustrates the complexity of protein modifications and their consequences: there are different oxPTMs, such as citrullination and glyoxidation, on both the proteins collagen and fibrinogen, and all can activate other immune cells. So far, a causative protein entity has not been identified, and no particular oxidative PTM has been found to induce RA disease. Additionally, RA is characterized by a heavy immuno-infiltrate that may contribute to disease pathogenesis. In RA, but also in other autoimmune disorders, oxidative PTMs play a critical role during development and progress [61]. Recent work increasingly focuses on the immunogenic properties of proteins and peptides that are not only present in the extracellular space as a consequence of tissue injury but also presented on the cell surface.

Table 1. Protein post-translational modifications (PTMs) linked to the cause of disease.

Modification	Protein	Disease	References
carbamylation	several	aging	[58,59]
carbonylation	E-FABP	diabetes	[62]
citrullination	Fibrinogen	RA	[63]
citrullination	Collagen	RA	[64–66]
deamination	Chromogranin A	Diabetes	[67]
hyperphosphorylation	Tau	Alzheimer's	[68,69]
oxidation	LDL	atherosclerosis	[70–72]
oxidation	laminin	Cardiovascular disease	[73]

4. Use of oxPTMs as Disease Biomarkers

Modified structures on the cell surface are characteristic footprints for some diseases and targets to trigger or block an immune response. Therefore, oxPTMs might be advantageous for disease diagnosis. For example, oxidation of low-density lipoprotein (LDL) has been proposed as a primary biomarker for diabetes [74] and cardiovascular diseases [75]. Furthermore, oxidation and chlorination of the extracellular matrix protein laminin were suggested as markers for cardiovascular disease and particularly atherosclerosis [73]. Just as LDL and laminin are anchored in the membrane and are accessible from outside, the major histocompatibility complex (MHC) is located on the cell surface to enable interaction with cells of the adaptive immune system. Each cell degrades intracellular proteins, loads the resulting fragments onto MHC, and presents it on the cell surface. Once a trafficking T cell recognizes the MHC structure, the receptor matches the MHC-bound protein fragment (epitope) as being of self- or non-self-origin. Epitopes of natural intracellular proteins are identified as “self”, and no immune response is triggered.

In contrast, PTMs on epitopes make them differ from their native forms and hence can generate foreign structures, allowing them to become a target of an immune response (Figure 2).

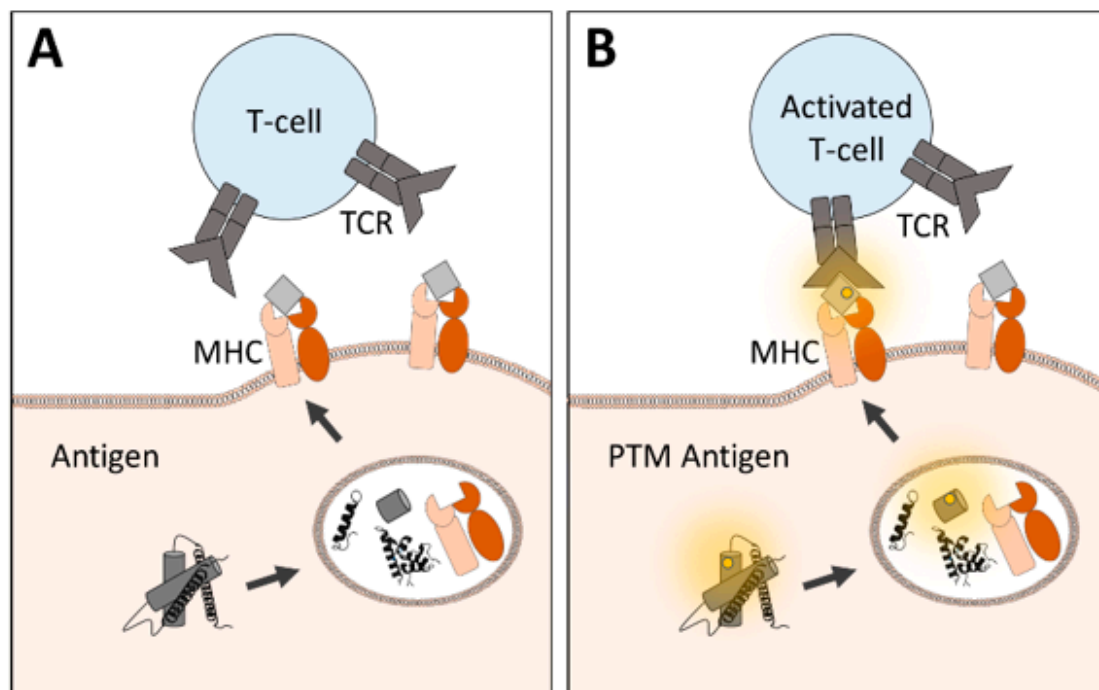


Figure 2. Immunogenicity of native and modified peptides is presented via major histocompatibility complex (MHC). T cells express antigen-specific receptors (TCR) with a specific binding site for MHC-presented peptides. While (A) native structures may not induce T cell activation, (B) post-translational modified peptides enable an altered binding affinity leading to an immune response.

In some cases, such as cancers, PTMs on epitopes which differ from the current host proteins might even serve to amplify an immune response leading to the eradication of unwanted cells. However, in autoimmune diseases, immune cells falsely attack host structures because PTM epitopes are presented and can lead to a break of tolerance [76], as seen in diabetes type I [77]. Not only in diabetes but also in other autoimmune disorders, PTM epitopes are suspected. Since the direct detection of native and PTM epitopes is difficult due to the isolation and qualification, indirect evidence is usually provided. In RA, T cell activation is the consequence of PTMs, such as carbamylation, citrullination, deamidation, or acetylation [78–81]. Moreover, B cells release autoantibodies that are specific for PTMs, leading to the attack of host proteins and structures [64,82–84]. Targeting those antibodies with neutralizing citrullinated peptides became a pioneering therapy option [63,85], suggesting a role of oxPTMs as therapeutics (Table 2).

Table 2. Using or targeting protein PTMs to control the disease.

Disease	Protein	PTM	Therapy	References
Allergy	Several	unknown	Modified allergen	[86,87]
Alzheimer's	Tau	hyperphosphorylation	Native Tau vaccine	[88,89]
Diabetes	Insulin B-Chain	-	Native antigen vaccine	[90,91]
Rheumatoid Arthritis	Fibrinogen, Collagen	citrullination	Anti-citrullin antibodies	[63,92]
Tumors	several	chlorination, others	Oxidized lysate vaccine	[93,94]

Intracellular proteins with putative PTMs are degraded and loaded onto MHC, where they can serve as an antigenic or tolerogenic peptide. It would, therefore, come as no surprise if epitopes with PTMs were also found in Alzheimer's patients since oxidatively modified proteins were identified in AD brains by proteomics analysis [95,96]. Since epitopes are structures that are recognized by immune cells, there are different therapeutic approaches to induce effective stimulation or inhibition

of their recognition. Not only are endogenous proteins degraded to be presented as peptides via MHC, exogenous proteins are also taken up by antigen-presenting cells, and peptides derived from exogenous proteins also bind to MHC, allowing immune cells to become primed for specific antigens. Thus, vaccination and immunotherapy with oxPTM proteins might be an alternative to antibody therapy.

5. Therapeutic Use of oxPTMs

Although the cellular mechanism and immune cell interactions are partly incompletely understood, increased immunogenicity of oxPTMs has been shown already in model systems of inflammation [97], diabetes [67], and allergy [98]. In such a way, not only PTMs, but also protein stability, adjuvants, or other companion substances (e.g., carrier proteins, nanoparticles) can increase the success of immunomodulatory therapeutics. There is a correlation between protein stability and immunogenicity [99], and PTMs can alter protein structure [14,100]. Thus, PTMs can also act as an adjuvant to improve protective immune response, as was shown for therapeutic vaccination for cancer therapy. Oxidatively modified tumor lysate reduced tumor growth and was more effective than injection with native tumor lysate [93,101–103]. This ultimately led to an increase of the anti-tumor T cell receptor repertoire and more durable and clinically apparent anti-tumor effects [94] (Figure 3A). Although tumor lysates consist of a pool of proteins that may mask the immunogenicity of individual proteins, vaccination with tumor-associated proteins alone has so far only generated little success [104,105]. Instead, typical tumor vaccines consist of either peptides, DNA, or mRNA, or are viral/bacterial-based with different advantages and disadvantages [106–110]. Non-enzymatic, oxidative PTM proteins or peptides have not come into focus, despite their expected relevance, as observed in inflammatory disease. By contrast, therapeutic vaccination in AD patients with the modified tau peptide or tau peptide in combination with adjuvants has led to vaccine-induced antibodies potentially targeting tau proteins [89,111,112]. It appears feasible to use such an approach in oncology also.

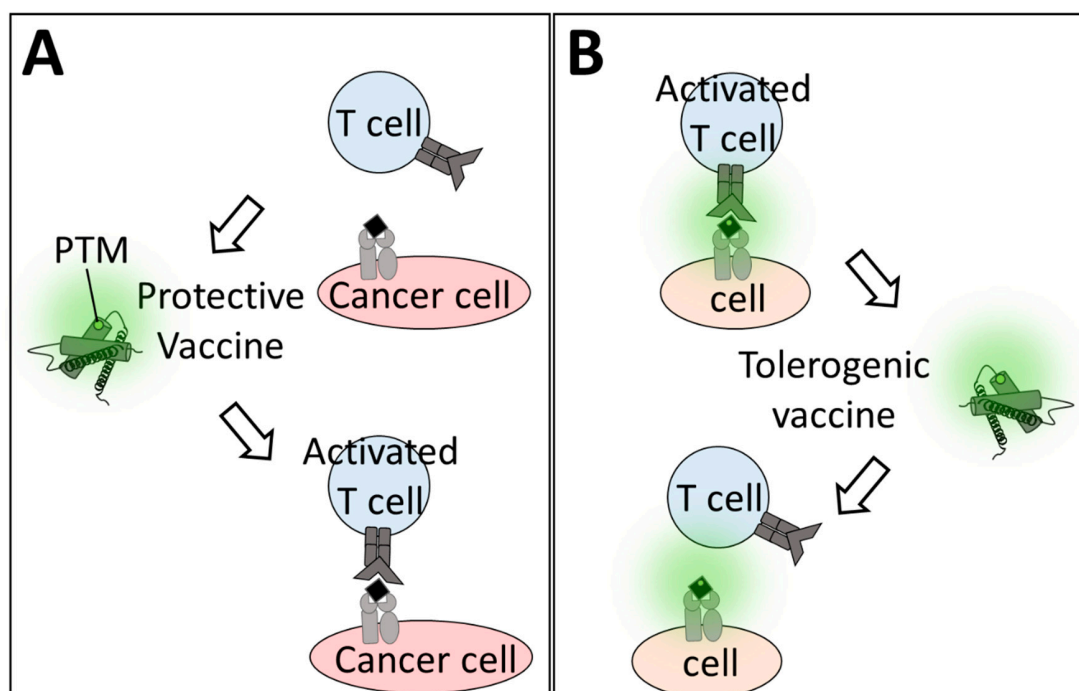


Figure 3. Modified proteins as therapeutics. Vaccination with oxPTM proteins alters antigen-specific T cell activation. **(A)** Cancer cells evade immune response due to the expression of “self” antigens, and the oxPTM vaccine enlarges the T cell repertoire to enable T cell activation. **(B)** In oxPTM-induced diseases, vaccination with modified proteins can dampen by increasing the threshold that is needed for activation.

In allergy, the goal is not to amplify but to dampen antigen-specific immune responses. Antigen-specific immune cell tolerance is achieved via antigen-specific regulatory T cells (T_{regs}) [113,114] that, hence, are one target of tolerogenic vaccines for treating autoimmune diseases (e.g., diabetes type 1, multiple sclerosis) [91,115,116] (Figure 3B). Enzymatic or non-enzymatic PTMs may accelerate vaccination success since such vaccines might be able to address the T cells specific for PTM-carrying proteins that are not being targeted when using non-modified proteins or peptides. For example, immunotherapy with modified peanut extract reduced allergenicity in peanut-allergic mice [86,87]. Studies with modified allergens in patients are challenging and have not yet been completed [117,118]. Assuming that the modified-allergen vaccine reduces allergenicity, further research should be done to identify the mechanistic basis of immunogenic vs. tolerogenic non-enzymatic protein modifications.

6. Gas Plasma Technology as an Innovative Tool for oxPTM Research

Inflammation generates different types of ROS [119], such as nitric oxide, hypochlorous acid, nitrite, superoxide anion, hydrogen peroxide, peroxyxynitrite, and nitrite. Chronic inflammation leads to constant ROS production, which is associated with inflammatory disease and autoimmunity [61] as well as carcinogenesis [120]. As outlined above, there is ample evidence that oxPTMs are critical in these processes. Studying oxPTMs, however, is challenging because modeling the multi-ROS environment in inflammatory tissues is limited by chemical restraints. Gas plasma technology overcomes this hurdle by generating a multitude of ROS simultaneously. Using cysteine as a model molecule, we have provided evidence that the oxPTMs created with plasma treatment are the consequences of different reactive species. Moreover, the oxPTM pattern can be controlled by modulating the ROS-output of the plasma systems [121]. Hence, gas plasma technology is an ideal tool for studying the tolerogenic and immunogenic oxPTM patterns on target proteins.

7. Conclusions

Changes in the immunogenicity of proteins based on post-translational modifications can not only cause but also potentially control several diseases. Although PTMs are currently underrepresented in therapeutic schemes in inflammation, autoimmunity, and cancer, evidence points to their pivotal role and significance in disease modulation. In this regard, gas plasma technology might be a potent tool to generate oxPTM patterns on proteins, allowing studies to be done on their tolerogenic or immunogenic nature in many diseases in future research.

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