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Role of oxidative stress in chemical allergens induced skin cells activation

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ABSTRACT

Allergic contact dermatitis (ACD) is an important occupational and environmental disease caused by topical exposure to chemical allergens. It describes the adverse effects that may results when exposure to a chemical elicits a T cell-mediated inflammatory skin disease. The ability of contact sensitizers to induce the oxidative stress pathway in keratinocytes and dendritic cells has been confirmed by several authors. Reactive oxygen species (ROS) can serve as essential second messengers mediating cellular responses resulting in immune cells activation. Oxidative stress may be the starter point, as it leads to the activation of transcription factors and signaling pathways, including NF-kB and p38 MAPK, which leads to the release of cytokines and chemokines. ROS are also involved in the activation of the NLRP3/NALP3 inflammasome, which is required to direct the proteolytic maturation of inflammatory cytokines such as IL-1β and IL-18, which are all integral to the process of dendritic cells mobilization, migration and functional maturation. Moreover, emerging evidence correlates ROS to changes in the constitution of the extracellular microenvironment found to facilitate ACD. The purpose of this review is to provide both conceptual and technical frameworks on the role of oxidative stress in chemical allergy.

1. Introduction

Irritant and allergic contact dermatitis are undesired side effects in the development of drugs and cosmetics as well as after contact with environmental or industrial chemicals. A recent epidemiological study of the general population suggests that the prevalence of contact allergy to at least one sensitizing chemical is ~15–20% (Peiser et al., 2012; Thyssen et al., 2007), making contact allergy a common and important environmental and occupational health hazard.

Whereas irritant contact dermatitis is a skin inflammation induced by primary contact with chemicals, and it is not mediated by lymphocytes, allergic contact dermatitis represents a delayed type hypersensitivity reaction caused mainly by reactive T helper 1 and interferon (IFN)-γ producing $CD8^+$ T cells (Tc1), which requires previous sensitisation by the same chemicals (Cavani et al., 2007; Basketter et al., 2008; Nosbaum et al., 2009). Contact hypersensitivity can occur as a result of exposure to a wide variety of chemicals and drugs (Nethercott and Holness, 1989), cosmetics (De Groot et al., 1988), and various metals including nickel (Picardo et al., 1990) and chromium (Nethercott and Holness, 1989). More than 3000 chemicals have been shown to cause skin sensitisation. In Fig. 1 a schematic representation of the key passages involved in the induction of chemical-induced skin sensitisation is depicted. In order for a chemical to induce skin sensitisation, it must satisfy certain requirements (key passages). Following absorption through the stratum corneum and gain access to the viable epidermis (usually chemical allergens have low molecular weight, <1000 Dalton, and appropriate lipophilicity, i.e. LogP ~2), as chemicals themselves are too small to cause an immunogenic reaction, they must bind to extracellular and cellular skin proteins to form a complete antigen. The development of allergic contact dermatitis then requires the activation of innate immune cells, including keratinocyes (KC) required for maturation and migration of dendritic cells (DC), and DC, required for the activation of T cells. For organic chemical allergens it is known that they fail to fully activate human or mouse DC in vitro, it is the skin microenvironment that provides the danger signals or DAMPs (damage associated molecular patterns), including ROS, uric acid, hyaluronic acid fragments and ATP, required for activation of pattern recognition receptors (PRRs) and full activation of DC, leading the up-regulation of the co-stimulatory molecules CD40, CD80 and CD86. The acquisition of specific immune response will then take place at the level of

Abbreviations: DC, dendritic cells; IL, interleukin; KC, keratinocytes; ROS, reactive oxygen species.

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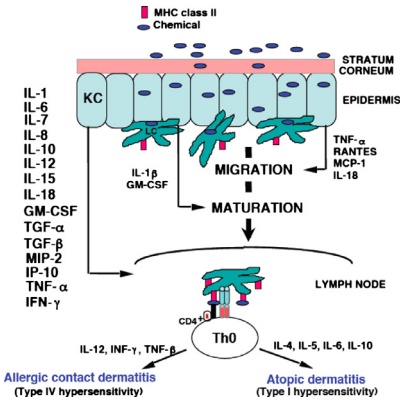

KEY PASSAGES

1. Absorption and local trauma — proinflammatory cytokine production by keratinocytes (KC), and release of danger signals and damage associated molecular patterns, including ROS, uric acid, hyaluronic acid fragments, ATP, HMGB1, etc.

2. Protein binding and formation of a complete antigen

3. Antigen processing

4. Langerhans cells (LC)/dermal dendritic cells (DC) maturation and migration

5. Antigen presentation to Th cells and generation of memory and effector T cells (immunogenicity)

Fig. 1. Key passages in the induction of skin sensitisation.

draining lymph nodes, where DC migrate via the afferent lymph vessels and stimulate the activation of hapten-specific responsive T-cells and the generation of Tc1 effector cells. Upon renewed contact with the same chemical, memory T cells are recruited to the site of contact, where interactions between T cells and antigen presenting cells can take place directly in the skin, thus initializing the inflammatory reaction (elicitation phase).

It is important to stress that hypersensitivity reactions are the result of normally beneficial immune responses acting inappropriately toward harmless chemicals, which are 'smelled' as pathogens in some individuals (Corsini and Kimber, 2007). In other words, chemical allergens mimick infection by triggering innate immune responses via pattern recognition receptors and endogenous danger signals, inducing 'sterile inflammation' (Martin, 2012).

1.1. Role of Ros and oxidative stress in contact allergy

Evidence indicates that allergic and inflammatory skin diseases are mediated by oxidative stress (Okayama, 2005; Byamba et al., 2010). Proteomic and genomic analyses of human keratinocytes as well as of dendritic cells revealed large numbers of clearly sensitizer-specific markers, with several interesting overlaps. Particularly, markers relating to the Nrf2-mediated oxidative response and oxidative stress in general were identified repeatedly, very much in line with the prominent position that oxidative stress holds in chemical sensitisation (Ryan et al., 2004; Ade et al., 2009; Hooyberghs et al., 2008; Johansson et al., 2011; Van der Veen et al., 2013).

Electrophilicity is one of the most common features of skin contact sensitizers and it is necessary for protein haptenation. The Keap1 [Kelch-like ECH-associated protein 1]/Nrf2-signaling pathway is dedicated to the detection of electrophilic stress in cells leading to the upregulation of genes involved in protection or neutralization of chemical reactive species. Several Authors have proposed that monitoring of this pathway may provide new biomarkers (e.g., Nrf2, hmox1) for the detection of the sensitisation potential of chemicals both in KC and DC (Natsch and Emter, 2007; Ade et al., 2009). A significant inhibition of the expression of oxidative stress associated genes and CD86 expression was observed by preincubated with N-acetyl cysteine, a glutathione precursor used to reinforce the redox potential of cells, further supporting the role of oxidative/electrophilic stress in chemical allergen-induced DC activation. Mizuashi et al. (2005) showed in human monocyte-derived dendritic cells that chemical sensitizers induced oxidative stress measuring the glutathione GSH/GSSG ratio, as a redox marker. These authors also showed that reduction of the glutathione GSH/GSSG ratio was accompanied by CD86 upregulation and p38 mitogen-activated protein kinase (p38 MAPK) activation, suggesting that the electrophilic properties of chemical sensitizers may be perceived by DCs as a danger signal leading to DC maturation (Sasaki and Aiba, 2007).

ROS have long been considered as harmful by-products of endogenous oxygen metabolism or cellular responses to hazardous agents. ROS have been implicated in the pathogenesis of several disorders, including cancer, aging, atherosclerosis, chronic inflammation, etc. (Brieger et al., 2012; Kleikers et al., 2012; Sosa et al., 2012). It is now known that ROS at relatively low concentrations also serve as essential second messengers mediating cellular responses to many physiological stimuli (Lenaz, 2012). It is now understood that ROS are critical mediators of intracellular signaling. ROS are products of normal cellular metabolism and under physiological conditions, participate in maintenance of cellular 'redox' homeostasis. Overproduction of ROS, results in oxidative stress. Within the cell, ROS are mainly generated by mitochondrial electron transport systems I and III, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, xanthine oxidase, nitric oxic synthase, cyclooxigenase, peroxisomes, cytochrome P-450 and ribonucleotide reductase systems. The NADPH oxidase, first identified in phagocytes and now found in virtually every tissue, is an example of a system that generates ROS not as a byproduct, but rather as the primary function of the enzyme system. A large number of scientific studies have highlighted the importance of ROS as a second messenger in numerous cellular processes, including cell proliferation, gene expression, adhesion, differentiation, senescence, and apoptosis. The thiol/disulfite status of cysteine residues of cellular proteins is counterregulated by ROS and by endogenous disulfite reductase systems, and this redox regulation tightly controls transcriptional activities of transcription factors, including AP-1 and NF-B, as well as catalytic potentials of protein kinases and phosphatases and proteins more directly involved in oxidative stress detection (Keap-1 [Kelch-like ECH-associated protein 1]/Nrf2, hypoxia inducible factor-1, thiore-doxin) (Cosentino-Gomes et al., 2012).

Within the immune system, ROS, besides acting as direct bacterial killing mechanisms, also stimulate the immune response through activation of signaling pathways, upregulation of surface co-stimulatory molecules, protein carbonylation, and cytokines secretion (Larbi et al., 2007; Sareila et al., 2011; Bertolotti et al., 2012). Amongst the mediators speculated to affect initial allergen sensitisation and the development of pathogenic allergic responses