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Current Opinion in Immunology

Interplay of innate and adaptive immunity in metal-induced hypersensitivity

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Metal-induced hypersensitivity is driven by T cell sensitization to metal ions. Recent advances in our understanding of the complex interactions between innate and adaptive immunity have expanded our knowledge of the pathogenesis of these diseases. Metals activate the innate immune system through direct binding to pathogen recognition receptors, activation of the inflammasome, or the induction of cellular death and release of alarmins. Certain metals can serve as adjuvants, promoting dendritic cell activation and migration as well as antigen presentation to metal-specific T cells. These T cells can recognize metals as haptens or as altered MHC-peptide complexes. The ability of metals to create these neoantigens emphasizes the similarity between metal-induced hypersensitivity and autoimmunity.

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Current Opinion in Immunology 2016, **42**:25–30

This review comes from a themed issue on **Allergy and hypersensitivity**

Edited by **James McCluskey** and **Robyn E O'Hehir**

http://dx.doi.org/10.1016/j.coi.2016.05.001

Introduction

Metals are ubiquitous substances in the environment, and metal ions in aqueous solution interact with molecules in living organisms. Accordingly, many metals such as chromium, copper, cobalt, iron, magnesium, manganese, molybdenum and zinc are essential for important biological processes, serving as cofactors for enzymes, impacting nucleic acid tertiary structure and facilitating oxygen transport [1]. In some cases, however, metals interact with biological molecules and disrupt their function, acting as irritants by initiating tissue injury and cellular death or generating inappropriate immune responses. The latter results in metal-induced hypersensitivity, a type IV delayed-type hypersensitivity response that is mediated by T cells reactive to metal ions. Sensitization of metal-reactive T cells requires disruption of barrier function, activation of innate pattern recognition receptors (PRRs), and interaction of metal ions with MHC/peptide complexes presented by dendritic cells (DCs) to naive T cells. These events lead to the expansion and survival of metal-reactive memory T cells that circulate throughout the body. Upon re-exposure to the metal or at sites where metals are not cleared, T cells may be reactivated to release cytokines that promote cellular damage and inflammation. In the case of skin exposure, this may lead to contact dermatitis. With lung exposure, metal ion sensitization promotes alveolitis that can progress to granulomatous inflammation and pulmonary fibrosis.

In the last several years, studies have revealed that metal-induced hypersensitivity involves disruption of homeostatic mechanisms that exist to prevent inappropriate immune responses to innocuous substances. Interestingly, although the mechanism is unclear, individuals with autoimmunity are more susceptible to metal-induced hypersensitivity [2•]. Metals that bind to the MHC/peptide complex within the TCR footprint can generate neoantigens that are recognized as foreign, thus blurring the distinction between hypersensitivity and autoimmunity [3••]. Genetic susceptibility to some metal-induced hypersensitivities is associated with the expression of certain MHCII alleles. For example, susceptibility to beryllium-induced hypersensitivity is strongly linked to *HLA-DPB1* alleles expressing a glutamic acid at the 69th position of the β-chain [4,5]. Metals may also serve as adjuvants by engaging innate PRRs and promoting DC activation and maturation. Insights into these mechanisms further our understanding of how small molecules generate hypersensitivity. We will highlight recent studies that have clarified how metals interact with the innate and adaptive arms of the immune system to drive the development and maintenance of these inappropriate immune reactions in genetically-susceptible individuals.

Recognition of metals by the innate immune system

Innate and adaptive immunity are involved in the initiation of metal-induced hypersensitivity [6]. However, a prerequisite is the penetration of physical barriers by metal ions and particles, which can occur via multiple routes including direct skin contact and inhalation into the lungs. Nickel is the most common cause of contact dermatitis, impacting ~15% of the population [7,8].

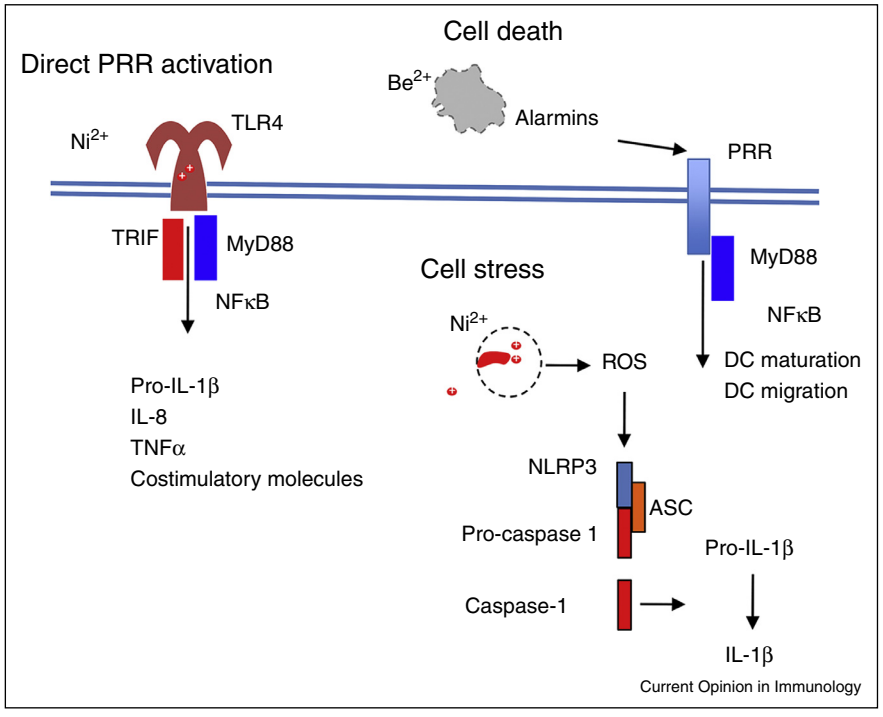
Chromium, palladium, cobalt are also common sensitizers [8,9]. Metal ions can directly penetrate the water-resistant stratum corneum barrier of the skin [10]. Pulmonary exposure via inhalation of metal particles or vapors is another route of sensitization. In particular, occupational exposure to beryllium-containing metals and cobalt/tungsten alloys can lead to sensitization and pulmonary disease [11,12].

Immunization with peptides or proteins in the absence of innate receptor activation induces tolerance [13]. Conversely, when combined with substances that activate innate PRRs, these receptors promote activation and migration of DCs from the site of exposure to the draining lymph nodes (LNs). Recent studies have shown that many metals can intrinsically activate PRRs and have their own adjuvant function. This occurs via three separate mechanisms: 1) direct interaction with PRRs, 2) induction of cellular stress and activation of reactive oxygen species (ROS) and the inflammasome and 3) induction of necrotic or NETotic cellular death and release of alarmins that activate PRRs (Figure 1).

Direct engagement of TLR4, a PRR that recognizes bacterial LPS and endogenous Damage-Associated Molecular Patterns (DAMPs), may play a role in nickel, cobalt and palladium-induced hypersensitivity. Nickel ions bind to histidine residues (e.g., H431, H456 and H458) on human TLR4, the latter two being conserved in primates, but not mice. This binding cross-links TLR4 inducing activation of NF-κB and release of TNF-α and IL-8 [14••,15•]. Accordingly, transgenic expression of human TLR4 in mice enhanced the development of nickel-induced hypersensitivity. Thus, nickel has intrinsic adjuvant properties in humans that promote sensitization of T cells. Similarly, cobalt and palladium ions also induce TLR4-dependent signaling [16,17].

Cellular stress results in activation of Nod-like receptor (NLR) members of the PRR family. Release of biologically active IL-1β requires two pathways. Activation of TLRs or cytokine receptors (IL-1R, IL-18R) that signal through MyD88 induces expression of pro-IL-1β. Activation of NLRs induce assembly of the inflammasome and activation of caspase-1 that cleaves pro-IL-1β into biologically-active IL-1β. There are multiple NLR family members including NLRpyrin (NLRP) proteins and NLRC4 (also called IPAF) that drive caspase-1 activity. Nickel ions induce activation of NLRP3 in murine bone marrow-derived DCs by inducing mitochondrial stress and release of ROS [18]. Cobalt, chromium, and molybdenum ions as well as cobalt alloy particles induce

Figure 1



Metals can induce PRR signaling through three separate pathways. The first mechanism is via direct activation of pattern recognition receptors, such as Ni-induced TLR4 activation. The second mechanism is via cellular stress following exposure of a cell to metal ions or particles, which leads to release of ROS and activation of the inflammasome. The final mechanism is via alarmins that are released as a result of necrotic cellular death and subsequent activation of PRRs.