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Interplay of innate and adaptive immunity in metal-induced hypersensitivity

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Abstract

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.

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-

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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-DPBI* 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- κ B 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-1 β requires two pathways. Activation of TLRs or cytokine receptors (IL-1R, IL-18R) that signal through MyD88 induces expression of pro-IL-1 β . Activation of NLRs induce assembly of the inflammasome and activation of caspase-1 that cleaves pro-IL-1 β into biologically-active IL-1 β . 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 secretion of IL-1 β via activation of the NLRP3 inflammasome by inducing lysosomal damage and release of ROS in human macrophages [19]. However, it is not known whether these metals activate ROS/NLRP3 inflammasomes in vivo or whether this pathway is required for the generation of hypersensitivity. While IL-1R signaling has been shown to be important in murine models of nickel-induced hypersensitivity [20], release of biologically-active IL-1 α is not dependent upon the inflammasome and could account for these effects [21]. For example, beryllium exposure in the lung induced rapid release of IL-1 α and not IL-1 β ; however, after long-term exposure to beryllium, IL-1 β is released [22,23]. Thus, other factors besides beryllium may be involved or required for priming of the pro-IL-1 β signal. We confirmed that IL-1 α was released in caspase-1KO mice exposed to beryllium and that neutrophil recruitment was similar in WT and caspase-1KO mice but absent in IL-1RKO mice [22]. Finally, the effects of beryllium-induced exposure on DC migration and CD4⁺ T cell priming capacity were not dependent upon IL-1R, caspase-1 or NLRP3[22]. Thus, although IL-1 β and the inflammasome are induced after chronic exposure to beryllium and may participate in chronic pulmonary inflammation, they are likely not required for beryllium sensitization.

Exposure to metals that result in cellular death promotes inflammation and activation of innate PRRs. For example, pulmonary exposure to beryllium in mice results in cellular death and rapid release of alarmins including DNA and IL-1 α into the alveolar space and enhanced migration of pulmonary DCs from the lung to the draining LNs via a MyD88-dependent pathway [22]. Accordingly, beryllium acts as a CD4⁺ T cell adjuvant in WT but not MyD88KO mice. However, multiple MyD88-dependent pathways are likely involved, as TLR9 deficiency was only associated with a partial impact on DC migration while TLR2, 4 and 7 were not required.

Dendritic cells and T cell sensitization

Under steady state conditions, DCs play a critical role in maintaining peripheral tolerance [24]. Engagement of cognate T cell receptors (TCRs) with MHC/peptide complexes presented by steady state DCs initiates proliferation and either activation-induced cell death

or energy. Conversely, when innate PRRs are directly engaged on DCs, activation of intracellular signaling pathways drives enhanced expression of costimulatory molecules [13]. These proteins deliver critical survival signals to T cells during a primary response. Following T cell activation with adequate costimulation, T cells differentiate into effector or memory cells that circulate through peripheral tissues.

DCs that reside in the skin include Langerhans cells in the epidermis and two subsets of dermal DCs, langerin⁺ dermal DCs and langerin^{neg} dermal DCs (Figure 2) [25]. Migration of DCs from the skin to the draining LNs is required for sensitization with other peripheral antigens including small molecule contact sensitizers [26]. Mice depleted of Langerhans cells have exaggerated hypersensitivity responses to contact sensitizers via a mechanism that involves MHCII presentation and IL-10 secretion, suggesting that Langerhans cells restrain responses to innocuous substances [27]. The role of specific dermal DC subsets is less clear, but dermal DCs appear to be involved in sensitization during contact hypersensitivity [28].

Pulmonary DCs consist of two major subsets, CD11b^{hi} DCs and CD103⁺ DCs. CD103⁺ DCs are specialized to ingest apoptotic cells and present cell-associated antigen to CD8⁺ T cells, while both subsets can prime CD4⁺ T cells (Figure 2) [29]. In mice exposed to beryllium, both subsets migrate into the lung-draining LNs and upregulate expression of CD80 and CD86 [22]. These effects are MyD88-dependent and result in enhanced priming of CD4⁺ T cells. Beryllium may also have direct impacts upon contact with DCs, including phosphorylation of MAP kinase p38, NF- κ B activation and enhanced stimulation of IFN- γ and TNF- α by Be-specific effector CD4⁺ T cells in vitro [30].

Presentation of metal ions to T cells via MHC molecules

Activation of T cells is critical for metal-induced hypersensitivity. Activation of naive T cells requires engagement of TCRs with MHC/peptide complexes expressed on the surface of DCs. Metal ions and other small molecule sensitizers interact with MHC/peptide complexes in a variety of ways to provide this signal. Some metal cations act as haptens by interacting with amino acid residues on MHC-bound peptides; certain nickel-reactive T cell clones recognize nickel via this mechanism [31,32]. In other cases, nickel promotes peptide independent cross-linking of the TCR and MHC molecules, similar to a superantigen [33]. Metal ion interactions with MHC may also alter the peptide repertoire of the MHC molecule [34]. Recently, a novel mechanism was shown where beryllium binds to HLA-DP2 and a bound self-peptide [35], altering the charge and conformation of the MHCII/peptide complex and generating a neoantigen [3]. In this case, the TCR contacted the altered region of HLA-DP2/peptide complex with no direct contact with the beryllium cation, which was buried beneath the self-peptide [3]. Several of these mechanisms involve altering previously tolerated MHC/peptide complexes in the periphery, thereby bypassing the ability of the thymus to negatively select against these T cell clones. In this way, metal-induced immune responses are directed against neoantigens. In addition, the ability of metals to act as adjuvants likely contributes to disrupting peripheral tolerance. Other small molecules or drugs also drive inappropriate T cell responses via similar mechanisms [36].

Effector T cells in the elicitation phase of hypersensitivity

CD4⁺ and CD8⁺ T cells play a role in contact dermatitis initiated by nickel, cobalt and palladium [6]. In contrast, CD4⁺ cells polarized towards a Th1 phenotype are strongly implicated in the pathogenesis of chronic beryllium disease (CBD) [4]. These beryllium-specific CD4⁺ T cells in bronchoalveolar lavage (BAL) of CBD patients express markers of previous activation [37,38], recognize beryllium in a CD28 costimulation-independent manner [39] and exhibit an effector memory T cell phenotype [37,40]. Studies of TCR expression on CD4⁺ T cells from ex vivo BAL of CBD patients demonstrated the presence of oligoclonal T cell populations that were specific for CBD and not seen in other lung diseases such as sarcoidosis [41,42], and these oligoclonal T cells were composed of beryllium-specific public CD4⁺ T cells, meaning that these T cells expressed identical TCR V α and/or V β genes and were present in the majority of CBD subjects [43]. In addition, their frequency inversely correlated with loss of lung function, suggesting that these beryllium-specific CD4⁺ T cells are pathogenic in nature [43].

Effector T cells recirculate to the site of metal exposure during the elicitation phase. In the case of skin exposure, this might involve release of IFN- γ or activation of cytotoxic CD8⁺ T cells that induce pruritus and rash. In the case of the lung or other target organs, this may involve the development of granulomatous inflammation as the T cells attempt to wall off the persistent metal and regulate inflammation. In addition to effector cells, regulatory T cells can be induced by metal ions and regulate inflammation [23]. As tissue damage progresses, deposition of collagen and fibrosis impairs organ function, leading to progressive disease and, in some cases, death.

Conclusions

Recent work has indicated that both the innate and adaptive arms of the immune system are required for development of hypersensitivity. Some metals, either in ion or particulate form that penetrate physiological barriers, act as intrinsic adjuvants by promoting signals through PRRs. At low dose exposure, this may lead to self-resolving subclinical inflammation. However, in genetically-susceptible individuals in whom metal ions associate with MHC/peptide molecules in a manner that drives TCR signaling, an elicitation phase occurs in which a pool of metal-reactive effector T cells orchestrate inflammation at sites of metal ion depots or re-exposure.

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References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Maret W. The Metals in the Biological Periodic System of the Elements: Concepts and Conjectures. *Int J Mol Sci.* 2016;17.
- 2•. Stejskal V, Reynolds T, Bjorklund G. Increased frequency of delayed type hypersensitivity to metals in patients with connective tissue disease. *J Trace Elem Med Biol.* 2015; 31:230–236. This study examined the frequency of metal hypersensitivity in patients with connective tissue disease (systemic lupus erythematosus, rheumatoid arthritis and Sjogren's syndrome) compared to a control group of healthy subjects. The authors found increased metal reactivity in the patients with connective tissue disease. [PubMed: 25636536]
- 3••. Clayton GM, Wang Y, Crawford F, Novikov A, Wimberly BT, Kieft JS, Falta MT, Bowerman NA, Marrack P, Fontenot AP, et al. Structural basis of chronic beryllium disease: linking allergic hypersensitivity and autoimmunity. *Cell.* 2014; 158:132–142. The authors crystallized the HLA-DP2-mimotope/beryllium complex interacting with a beryllium-specific TCR. Beryllium binding to the HLA-DP2-mimotope complex alters both the charge and conformation of the MHCII complex, and the TCR recognized this neoantigen with no contact with the beryllium cation. [PubMed: 24995984]
4. Fontenot AP, Falta MT, Kappler JW, Dai S, McKee AS. Beryllium-induced hypersensitivity: genetic susceptibility and neoantigen generation. *J Immunol.* 2016; 196:22–27. [PubMed: 26685315]
5. Richeldi L, Sorrentino R, Saltini C. HLA-DPB1 glutamate 69: a genetic marker of beryllium disease. *Science.* 1993; 262:242–244. [PubMed: 8105536]
6. Schmidt M, Goebeler M. Immunology of metal allergies. *J Dtsch Dermatol Ges.* 2015; 13:653–660. [PubMed: 26053629]
7. Hogeling M, Pratt M. Allergic contact dermatitis in children: the Ottawa hospital patch-testing clinic experience, 1996 to 2006. *Dermatitis.* 2008; 19:86–89. [PubMed: 18413109]
8. Mahler V, Geier J, Schnuch A. Current trends in patch testing - new data from the German Contact Dermatitis Research Group (DKG) and the Information Network of Departments of Dermatology (IVDK). *J Dtsch Dermatol Ges.* 2014; 12:583–592. [PubMed: 24981472]
9. Budinger L, Hertl M. Immunologic mechanisms in hypersensitivity reactions to metal ions: an overview. *Allergy.* 2000; 55:108–115. [PubMed: 10726725]
10. Bos JD, Meinardi MM. The 500 Dalton rule for the skin penetration of chemical compounds and drugs. *Exp Dermatol.* 2000; 9:165–169. [PubMed: 10839713]
11. Balmes JR, Abraham JL, Dweik RA, Fireman E, Fontenot AP, Maier LA, Muller-Quernheim J, Ostiguy G, Pepper LD, Saltini C, et al. An official American Thoracic Society statement: diagnosis and management of beryllium sensitivity and chronic beryllium disease. *Am J Respir Crit Care Med.* 2014; 190:e34–59. [PubMed: 25398119]
12. Seaman DM, Meyer CA, Kanne JP. Occupational and environmental lung disease. *Clin Chest Med.* 2015; 36:249–268. viii–ix. [PubMed: 26024603]
13. Medzhitov R, Janeway CA Jr. Innate immunity: impact on the adaptive immune response. *Curr Opin Immunol.* 1997; 9:4–9. [PubMed: 9039775]
- 14••. Schmidt M, Raghavan B, Muller V, Vogl T, Fejer G, Tchaptchet S, Keck S, Kalis C, Nielsen PJ, Galanos C, et al. Crucial role for human Toll-like receptor 4 in the development of contact allergy to nickel. *Nat Immunol.* 2010; 11:814–819. The authors show that human, but not mouse, TLR4 is activated by interaction of nickel ions with histidine residues in the receptor and that expression of human TLR4 in mice promotes development of nickel-induced hypersensitivity. [PubMed: 20711192]
- 15•. Raghavan B, Martin SF, Esser PR, Goebeler M, Schmidt M. Metal allergens nickel and cobalt facilitate TLR4 homodimerization independently of MD2. *EMBO Rep.* 2012; 13:1109–1115. This paper shows that similar to nickel, cobalt ions also induce activation of human TLR4 in a manner that depends upon H456 and 458. [PubMed: 23059983]
16. Potnis PA, Dutta DK, Wood SC. Toll-like receptor 4 signaling pathway mediates proinflammatory immune response to cobalt-alloy particles. *Cell Immunol.* 2013; 282:53–65. [PubMed: 23680697]
17. Rachmawati D, Bontkes HJ, Verstege MI, Muris J, von Blomberg BM, Scheper RJ, van Hoogstraten IM. Transition metal sensing by Toll-like receptor-4: next to nickel, cobalt and palladium are potent human dendritic cell stimulators. *Contact Dermatitis.* 2013; 68:331–338. [PubMed: 23692033]

18. Li X, Zhong F. Nickel induces interleukin-1 β secretion via the NLRP3-ASC-caspase-1 pathway. *Inflammation*. 2014; 37:457–466. [PubMed: 24158569]
19. Caicedo MS, Desai R, McAllister K, Reddy A, Jacobs JJ, Hallab NJ. Soluble and particulate Co-Cr-Mo alloy implant metals activate the inflammasome danger signaling pathway in human macrophages: a novel mechanism for implant debris reactivity. *J Orthop Res*. 2009; 27:847–854. [PubMed: 19105226]
20. Vennegaard MT, Dyring-Andersen B, Skov L, Nielsen MM, Schmidt JD, Bzorek M, Poulsen SS, Thomsen AR, Woetmann A, Thyssen JP, et al. Epicutaneous exposure to nickel induces nickel allergy in mice via a MyD88-dependent and interleukin-1-dependent pathway. *Contact Dermatitis*. 2014; 71:224–232. [PubMed: 25040758]
21. Eigenbrod T, Park JH, Harder J, Iwakura Y, Nunez G. Cutting edge: critical role for mesothelial cells in necrosis-induced inflammation through the recognition of IL-1 α released from dying cells. *J Immunol*. 2008; 181:8194–8198. [PubMed: 19050234]
22. McKee AS, Mack DG, Crawford F, Fontenot AP. MyD88 dependence of beryllium-induced dendritic cell trafficking and CD4⁺ T-cell priming. *Mucosal Immunol*. 2015; 8:1237–1247. This study showed that MyD88 is required for beryllium to enhance pulmonary DC migration to the draining lymph nodes and enhanced CD4 T cell priming. [PubMed: 25760420]
23. Mack DG, Falta MT, McKee AS, Martin AK, Simonian PL, Crawford F, Gordon T, Mercer RR, Hoover MD, Marrack P, et al. Regulatory T cells modulate granulomatous inflammation in an HLA-DP2 transgenic murine model of beryllium-induced disease. *Proc Natl Acad Sci U S A*. 2014; 111:8553–8558. This study showed that mice transgenic for the MHCII molecule, HLA-DP2, could generate an adaptive immune response to BeO exposure. [PubMed: 24912188]
24. Tsitoura DC, DeKruyff RH, Lamb JR, Umetsu DT. Intranasal exposure to protein antigen induces immunological tolerance mediated by functionally disabled CD4⁺ T cells. *J Immunol*. 1999; 163:2592–2600. [PubMed: 10452998]
25. Clausen BE, Stoitzner P. Functional Specialization of Skin Dendritic Cell Subsets in Regulating T Cell Responses. *Frontiers Immunol*. 2015; 6:534.
26. Forster R, Schubel A, Breitfeld D, Kremmer E, Renner-Muller I, Wolf E, Lipp M. CCR7 coordinates the primary immune response by establishing functional microenvironments in secondary lymphoid organs. *Cell*. 1999; 99:23–33. [PubMed: 10520991]
27. Igyarto BZ, Jenison MC, Dudda JC, Roers A, Muller W, Koni PA, Campbell DJ, Shlomchik MJ, Kaplan DH. Langerhans cells suppress contact hypersensitivity responses via cognate CD4 interaction and langerhans cell-derived IL-10. *J Immunol*. 2009; 183:5085–5093. [PubMed: 19801524]
28. Bursch LS, Wang L, Igyarto B, Kissenpfennig A, Malissen B, Kaplan DH, Hogquist KA. Identification of a novel population of Langerin⁺ dendritic cells. *J Exp Med*. 2007; 204:3147–3156. [PubMed: 18086865]
29. Desch AN, Randolph GJ, Murphy K, Gautier EL, Kedl RM, Lahoud MH, Caminschi I, Shortman K, Henson PM, Jakubczik CV. CD103⁺ pulmonary dendritic cells preferentially acquire and present apoptotic cell-associated antigen. *J Exp Med*. 2011; 208:1789–1797. [PubMed: 21859845]
30. Li L, Huang Z, Gillespie M, Mroz PM, Maier LA. p38 Mitogen-Activated Protein Kinase in beryllium-induced dendritic cell activation. *Hum Immunol*. 2014; 75:1155–1162. This paper shows that direct exposure of human dendritic cells to beryllium can drive activation of intracellular signaling molecules via an unknown receptor. [PubMed: 25454621]
31. Romagnoli P, Labhardt AM, Sinigaglia F. Selective interaction of Ni with an MHC-bound peptide. *EMBO J*. 1991; 10:1303–1306. [PubMed: 2026136]
32. Lu L, Vollmer J, Moulon C, Weltzien HU, Marrack P, Kappler J. Components of the ligand for a Ni⁺⁺ reactive human T cell clone. *J Exp Med*. 2003; 197:567–574. [PubMed: 12615898]
33. Gamerding K, Moulon C, Karp DR, Van Bergen J, Koning F, Wild D, Pflugfelder U, Weltzien HU. A new type of metal recognition by human T cells: contact residues for peptide-independent bridging of T cell receptor and major histocompatibility complex by nickel. *J Exp Med*. 2003; 197:1345–1353. [PubMed: 12756270]

34. Griem P, von Vultee C, Panthel K, Best SL, Sadler PJ, Shaw CF 3rd. T cell cross-reactivity to heavy metals: identical cryptic peptides may be presented from protein exposed to different metals. *Eur J Immunol.* 1998; 28:1941–1947. [PubMed: 9645376]
- 35••. Falta MT, Pinilla C, Mack DG, Tinaga AN, Crawford F, Giulianotti M, Santos R, Clayton GM, Wang Y, Zhang X, et al. Identification of beryllium-dependent peptides recognized by CD4⁺ T cells in chronic beryllium disease. *J Exp Med.* 2013; 210:1403–1418. This study was the first to delineate a complete $\alpha\beta$ TCR ligand for a metal-specific CD4⁺ T cell. [PubMed: 23797096]
- 36••. Illing PT, Vivian JP, Dudek NL, Kostenko L, Chen Z, Bharadwaj M, Miles JJ, Kjer-Nielsen L, Gras S, Williamson NA, et al. Immune self-reactivity triggered by drug-modified HLA-peptide repertoire. *Nature.* 2012; 486:554–558. This is an outstanding study that delineated the structural basis of the abacavir hypersensitivity syndrome. [PubMed: 22722860]
37. Fontenot AP, Canavera SJ, Gharavi L, Newman LS, Kotzin BL. Target organ localization of memory CD4⁺ T cells in patients with chronic beryllium disease. *J Clin Invest.* 2002; 110:1473–1482. [PubMed: 12438445]
38. Saltini C, Kirby M, Trapnell BC, Tamura N, Crystal RG. Biased accumulation of T lymphocytes with “memory”-type CD45 leukocyte common antigen gene expression on the epithelial surface of the human lung. *J Exp Med.* 1990; 171:1123–1140. [PubMed: 2139099]
39. Fontenot AP, Gharavi L, Bennett SR, Canavera SJ, Newman LS, Kotzin BL. CD28 costimulation independence of target organ versus circulating memory antigen-specific CD4⁺ T cells. *J Clin Invest.* 2003; 112:776–784. [PubMed: 12952926]
40. Fontenot AP, Palmer BE, Sullivan AK, Joslin FG, Wilson CC, Maier LA, Newman LS, Kotzin BL. Frequency of beryllium-specific, central memory CD4⁺ T cells in blood determines proliferative response. *J Clin Invest.* 2005; 115:2886–2893. [PubMed: 16151531]
41. Fontenot AP, Kotzin BL, Comment C, Newman LS. Expansions of T-cell subsets expressing particular T cell receptor variable regions in chronic beryllium disease. *Am J Respir Cell Mol Biol.* 1998; 18:581–589. [PubMed: 9533947]
42. Fontenot AP, Falta MT, Freed BM, Newman LS, Kotzin BL. Identification of pathogenic T cells in patients with beryllium-induced lung disease. *J Immunol.* 1999; 163:1019–1026. [PubMed: 10395700]
- 43•. Bowerman NA, Falta MT, Mack DG, Wehrmann F, Crawford F, Mroz MM, Maier LA, Kappler JW, Fontenot AP. Identification of multiple public TCR repertoires in chronic beryllium disease. *J Immunol.* 2014; 192:4571–4580. This study identified a beryllium-specific public CD4⁺ T cells whose frequency in BAL inversely correlated with lung function in a group of HLA-DP2-expressing CBD patients. [PubMed: 24719461]

Highlights

- Metal-induced hypersensitivity involves sensitization of metal-reactive T cells.
- Metals penetrate skin and lung barriers and interact with self-proteins and cells.
- Metals activate innate immune responses that may contribute to sensitization.
- Metals interact with MHCII/peptide complexes to activate CD4⁺ T cells.

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.

Figure 2. Model of metal-induced sensitization

Exposure of the skin or lung to metal ions or particles results in association of metal ions with MHC molecules on the surface of dendritic cells. Activation of pattern recognition receptors on either dendritic cells themselves or other cells at the site of exposure promotes migration of activated dendritic cells to the draining lymph nodes. Cellular death leads to the release of alarmins that engage PRRs. Langerhans cells impair the development of sensitization while dermal dendritic cells that migrate to the draining lymph nodes promote expansion of effector cells that drive inflammation and disease. In the lung pulmonary dendritic cells promote expansion of CD4⁺ T cells that circulate back to the lung and, in the case of chronic beryllium disease, mediate granuloma formation.