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Physiology and Pathology of Autoinflammation: NOD like Receptors in Autoinflammation and Autoimmunity

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Abstract

Immune regulation is an essential feature of immune responses. The failure of such regulation results in allergic reactions and debilitating autoimmune diseases that can be fatal. Furthermore, the recent increase in the prevalence of the latter as well as the medical severity makes this a subject of great medical interest. Autoimmunity results from a breakdown in or the failure of the self-tolerance mechanisms. Many genes have been identified in which mutations cause the predisposition to autoinflammation and autoimmunity in human and in animal models. The relatively small number of genes explored to date unquestionably shows the challenges of identifying the associated genes in outbred populations of humans. One chief contributing gene family to both autoinflammatory and autoimmune diseases is the nucleotide-binding and oligomerization domain (NOD)-like receptor (NLR) family. Ever since their discovery, NLRs have drawn considerable attention for their ability to form multiprotein complexes called inflammasomes and also for their roles as NLRs, independent of inflammasome complexes. We herein first revisit general characteristics of NLRs and inflammasomes. We then couple this knowledge with the most recent findings related to autoinflammatory and autoimmune diseases, while highlighting some unanswered questions and future perspectives in elucidating NLR roles in health and disease.

Keywords: NOD-like receptor signaling, inflammasomes, PAMPs, DAMPs, HAMPs, SAMPs, autoinflammation, autoimmunity

1. Inflammasomes and NOD-like receptors (NLRs)

Inflammasomes are nucleotide-binding and oligomerization domain (NOD)-like receptor (NLR) multiprotein complexes that activate the cysteine protease caspase-1 (IL-1 beta-converting enzyme) and then lead to the maturation of pro-IL-1 β and IL-18. Even though they

are the component of the innate immune system, their ability to regulate the adaptive immune system have been previously suggested (**Figure 1**) [1]. The immune system in mammals comprises a germline-encoded innate immune system and an acquired adaptive immune system that is able to eradicate pathogenic microorganisms with a sophisticated specificity and a long-term memory. The innate immune system is a primary role player in shaping host resilience. This system is armed with a broad portfolio of pattern recognition receptors (PRRs) that convert microbial and danger recognition into rapid host defenses as well as convey signals to prime the adaptive immune responses for a long-lasting protection. Nucleotide-binding and oligomerization domain (NOD)-like receptors (NLRs) are a class of evolutionarily conserved intracellular PRRs that play an important role in innate immunity and host physiology and also most recently in regulating and shaping adaptive immunity as predicted by their prevalence in organisms [2]. To date, there are 22 known NLRs in humans, and the single nucleotide polymorphisms (SNPs) in their genes as well as the association of mutations with human diseases emphasize their critical role in host defense.

Of the number of genes involved in the development of autoinflammatory and autoimmune diseases, some affect the cells of the immune system directly, changing the immunoreactivity of their host. These genes are mostly not disease-specific. This type of genes has been identified in mouse models as well. An excellent example for such a gene family is NLR-encoding gene family. NLRs are a special group of cytosolic proteins that play an important role in the regulation of host innate immune responses. They are expressed in lymphocytes, macrophages, dendritic cells (DCs) as well as in some non-immune cells such as epithelium [3]. In the most general terms, NLRs are classified into four subfamilies based on the structural similarities of their proteins: NLRA, acidic domain containing; NLRB, baculoviral inhibitory repeat (BIR) domain containing; NLRC, caspase activation and recruitment domain (CARD)

Figure 1. Activation of the inflammasome and its connections between the innate and adaptive immune system.

containing; NLRP, pyrin domain (PYD) containing; NLRX, with no strong homology to the N-terminal domain of any other NLR subfamily member [4]. After describing the subfamilies of NLR family members, based on the N-terminal region domain, we now describe the other essential domains. A typical NLR protein is composed of three domains. These domains are effector domains in N-terminal (PYRIN, CARD or BIR domains) as just been discussed, a central nucleotide-binding domain (NACHT or NOD domain) and a C-terminal leucine-rich repeats (LRRs). N-terminal effector domains are responsible for interacting with signaling molecules in downstream pathway [5]. The NACHT or NOD domain is responsible for oligomerization of protein and LRRs are required for identification of ligand molecules when there is a potential ligand. LRR domain, on the other hand, acts as a suppressor of NLR activation by preventing activation of the N-terminal domain when no ligand present in the environment, therefore playing a role in the autoregulation of these proteins [6]. Following ligand binding, the auto-regulatory LRR undergoes a conformational change, which then exposes the N-terminal domain, therefore, its interaction with downstream signaling adaptor proteins or effectors and finally the multiprotein complex formation [7, 8].

NLRC4, NLRP3, NLRP6, NLRP1, NLRP12, NLRP7 and the PYHIN family member AIM2 have been shown to form inflammasomes that play a critical role in recognizing pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs) and most recently homeostasis altering molecular processes (HAMPs) triggering the immune response [9–11]. Caspase-1 is necessary for the maturation of inflammatory cytokines IL-1 β and IL-18 from their pro-forms and eventually the induction of a cell death called as pyroptosis [9, 12]. During activation, the NLR triggers caspase-1 activation either directly by CARD-CARD interaction or indirectly through the adaptor molecule apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC). Caspase-1 then cleaves pro-IL-1 β and pro-IL-18 leading to their activation and secretion [13]. Although NLRs, including NLRC4, NLRP3, NLRP6, NLRP1, NLRP12, NLRP7 and the PYHIN family member absent in melanoma 2 (AIM2) are suggested to function by forming inflammasomes, other NLRs such as NOD1, NOD2, NLRP10, NLRX1, NLRC5 and CIITA do not function through the formation of inflammasomes but act via the activation of nuclear factor-kB (NF-kB), interferon (IFN) regulatory factors (IRFs) and mitogen-activated protein kinases (MAPKs) to induce innate immune responses [3].

As we will further discuss in the next topic, NLRs have the ability to recognize PAMPs and DAMPs which makes them remarkable molecules to set the activation threshold in case of an infection. Added to these mechanisms of recognition, HAMPs have strikingly, been postulated to have roles in the regulation of inflammasomes. According to the HAMP hypothesis, the pyrin domain (PYD) of a NLR protein is kept inert by a molecular pathway wherein the small GTPase RAS homologue gene family member A (RHOA) activates serine/threonine protein kinase N1 (PKN1) and PKN2, resulting in the subsequent phosphorylation of pyrin on serine 242 [14]. 14-3-3 proteins are a conserved protein family that play roles in many different cellular signaling pathways. They bind pyrin following its phosphorylation, maintaining its inactivated state. In the presence of a PAMP, such as *Clostridium difficile* toxin B (TcdB) pyrin is activated; however, this activation does not result in the activation of the immune system, because pyrin activation is dependent on the function of the toxin, not its structure. TcdB disrupts the RHOA phosphorylation pathway thereby leads to the removal of the 14-3-3, allowing the activation of pyrin (dephosphorylated state). By this mechanism, pyrin can respond to any

microbe infection that changes the RHOA, PKN1 and PKN2, as well as 14-3-3 activity. On the basis of pyrin's ability to sense the alterations in phosphorylation balance which is an altered homeostasis, pyrin is proposed to function not only as a universal sensor of extensive cellular changes, but also as a sensor for a single PAMP or DAMP [9]. This toxin function-based detection mechanism overrides the structural restrictions of the conventional PAMP recognition model. On the other hand, the model of HAMP recognition has some ramifications. A non-pathogenic agent might also alter the cellular phosphorylation processes which will lead to pyrin activation. Defective prenylation causes the inactivation of RHOA and therefore pyrin activation. These individuals with deficient protein prenylation develop hyper-IgG syndrome, which is considered as an auto-inflammatory disease [15, 16]. Sensing HAMPs through pyrin constitutes an example for the ability of NLRP1, NLRP3 and NLRP6 to respond to broad and diverse molecular stimuli. Although the most studied of these sensors is NLRP3, the complete molecular mechanism of action for NLRP3 activation is largely unknown. One of the most recent report demonstrated that NLRP3 is phosphorylated in a similar way to pyrin, suggesting that NLRP3 activation might require the detection of phosphorylation [17]. Furthermore, IL-1 β plays a role as an effector molecule as well as a HAMP sensor. Inactive forms of IL-1 β is cleaved by caspase-1 after the inflammasome assembly is complete. However, it should be noted that IL-1 β can also be cleaved by bacterial proteases. This notable adaptation aids in the efficient clearance of the bacteria. However, the mutations that were acquired by the pathogens can hinder the maturation of IL-1 β via cleavage by bacterial proteases [18], therefore they might enhance the invasion by bacteria. The use of IL-1 β -inhibiting drugs during infections, does not let the rise of such mutations. In this case, it is clear that activation of innate immune response depends on the detection of protease activity, meaning that the function but not the structure is the determinant of the inflammatory responses, another supporting evidence for the HAMP model. In contrast to the non-mammalian-derived PAMP detection point of view, HAMPs and DAMPs would most likely be generated in the absence of a pathogen, hence would increase the risk of inflammatory diseases and may theoretically contribute to the pathophysiology of inflammatory diseases. The nutrients, growth factors, oxygen and neighboring other cells, surrounding extracellular milieu maintain the homeostasis of cells. The alteration in the components of the environment such as pH, oxygen levels, temperature, concentration of certain molecules disturbs the physiological basal state of cells (i.e. the homeostatic balance) [19]. Altered homeostasis triggers a cellular stress response, resulting in the release of DAMPs as well as HAMP detection by pyrin. Recognition of stress by tissue macrophages activates signaling pathways, including inflammasomes, inducing an inflammatory response to recover tissue functionality during homeostatic imbalance. The inflammation dependent on the tissue-resident macrophages that induces an adaptive response is termed "para-inflammation" [20]. It has been proposed that the para-inflammation is of great importance to the chronic inflammatory responses that are associated with modern human diseases, like autoinflammatory and autoimmune diseases as well as the acute inflammatory responses that will damage the tissue [21]. Although the development of inflammatory diseases resulting from HAMP detection as a pathogen recognition system require more experimental data, ER stress-induced NLRP3 inflammasome activation in chronic liver diseases has been reported [22]. The new discoveries of inflammasome associations with inflammatory diseases remain to be of great interest, however; despite the incremental data, negative

regulation of inflammasome activation is still poorly understood. As the controlled inflammation is crucial to health, the mechanisms of inflammasome inactivation was evaluated and reported that NLRP3 inflammasome activation was dampened by protein kinase A (PKA), which phosphorylated NLRP3 and hindered its ATPase function. PKA phosphorylation was mediated by prostaglandin E₂ (PGE₂) signaling upon binding the PGE₂ receptor E-prostanoid 4 (EP4) [17]. In the negative regulation of NLRP3, Ser295 in human NLRP3 was found to be significant for immediate inhibition and PKA phosphorylation. The NLRP3-S295A mutation displayed a phenotype similar to the human cryopyrin-associated periodic syndrome (CAPS, an autoinflammatory disease) mutants. These data suggest that negative regulation at Ser295 is essential and important for restricting the NLRP3 inflammasome and define a molecular basis for NLRP3 mutations associated with CAPS [17]. Mutations and variations of NLR proteins are found to be significantly associated with autoinflammatory and autoimmune diseases (**Figure 2**). Another inflammasome is absent in melanoma 2 (hereafter AIM2). AIM2 recognizes dsDNA in a way that does not require a specific sequence. However, to be able to recognize the dsDNA, its length should be at least 80 base pairs [23]. Following DNA binding, AIM2 forms an inflammasome complex with ASC adaptor molecule and caspase-1, resulting in the maturation of pro-IL-1 β and pro-IL-18. Uncontrolled recognition of self dsDNA contributes to the development of autoinflammatory and autoimmune diseases such as psoriasis and dermatitis [24]. Importantly, polymorphisms or changes in expression of AIM2 have been associated with systemic lupus erythematosus (SLE) in humans [25]. In mice prone to lupus, inefficient degradation of self-DNA immune complexes in the lysosome let DNA enter the cytoplasm, which then activates the AIM2 inflammasome in macrophages [26, 27]. Vascular damage is one symptoms of SLE, and expression of AIM2 and IL-18 have been reported to increase in endothelial cells from patients with SLE as well as in a mouse model of SLE [28].

Figure 2. NOD-like receptor subfamilies associated with autoinflammatory and autoimmune diseases.

2. Pattern-associated molecular patterns (PAMPs)

The molecular characteristics of antigen recognition are remarkably different between adaptive and innate immune systems. In the adaptive immune system, random genomic recombination generates antigen receptors that recognize a wide range of antigens, while the innate immune system recognizes pathogens via a set of 20–40 pattern recognition receptors (PRRs) that are germline encoded. Each of these PRR proteins is specialized to recognize a relatively limited collection of pathogen-associated molecular patterns (PAMPs). The PRRs include the toll-like receptor (TLR), NOD-like receptor (NLR), RIG-I-like receptor (RLR) and C-type lectin receptor (CLR) families. Therefore, they are fixed and their ability to recognize rapidly evolving pathogens is quite limited [29, 30]. Sole reliance on recognition of the highly conserved PAMPs by PRRs constitutes a dangerous situation for the host. The past decade has seen a remarkable refocusing in immunology on the cells of the innate immune system, especially macrophages and dendritic cells. A preponderance of evidence suggests that the innate immune system holds more sophisticated recognition mechanisms than originally predicted. In addition to PAMPs, the alternative recognition system involves danger-associated molecular patterns (DAMPs); however, the DAMP molecules, such as ATP, uric acid crystals [31] and extracellular ATP, originate from self. This mechanism basically allows the innate immune system to sense cell death, bypassing the PAMPs [32]. Homeostasis-altering molecular processes (HAMPs) [9] are a newly emerging mechanism, distinct from DAMPs, proposed by Liston et al. Even though both DAMPs and HAMPs are specific to the host's own cells, DAMPs are recognized by PRRs in the same manner as the PAMPs. One important distinction of HAMPs is that, unlike PAMPs and DAMPs, they are not recognized by PRRs. They are the output of an alteration in homeostasis in a living cell, in which case, the innate immune system detects a cellular imbalance rather than a pattern. Intracellular inflammasome complexes provide excellent examples of this mechanism in action, as we discuss later in this chapter.

In contrast to foreign pathogen recognition through PAMPs by PRRs, there is an alternative mechanism for HAMPs (or DAMPs) that can cause inflammation in a sterile manner, resulting in tissue injury in the absence of a pathogen. This generates a potential link between HAMPs and (auto)-inflammatory diseases.

In addition to PAMPs, DAMPs and HAMPs, the term “SAMP” was introduced for self-associated molecular patterns, which could be sensed by innate inhibitory receptors to maintain a steady state level of immune cells and mitigate responses to self-molecule recognition (**Figure 1**) [12]. Host cells produce many different types of plasma membrane molecules that preclude complement reactions from occurring on their cell surfaces. The most important of these molecules is the carbohydrate moiety sialic acid, a common component of cell-surface glycoproteins and glycolipids. Given that they are abundant on cell surfaces and in the extracellular matrix, sialic acid as a self-glycan is the best candidate that fulfills the requirement to be a SAMP molecule. Other candidate SAMPs are glucose amino glycans (GAGs) such as sulfate heparin and dermatan sulfate [33]. As pathogens lack sialic acid, they are selected for destruction by complement pathway, while host cells are protected in the process. Some pathogens, including the bacterium *Neisseria gonorrhoeae* that causes the sexually transmitted disease gonorrhea, cover themselves

with a sialic acid layer to evade from the complement system. Hence, to recognize SAMPs, there might be self-PRRs (SPRRs). One suggested example is an innate component that inhibits the alternative complement pathway, called factor H (FH), which is a serum protein. FH inhibits the alternative complement pathway activation on host cell surfaces by detecting “self” in the form of sialic acid-bearing patterns on cell surfaces. Important residues in the sialic acid binding site are conserved from mouse to man, proposing a potential role for sialic acid as a host marker also in other mammals and a key role in human complement homeostasis [34]. FH recognizes heparin/heparin sulfate GAGs as well as sialic aiding host-non host discrimination by complement pathway [35]. Mutations in the critical residues that are involved in the binding of FH to the sialic acid have been shown to result in the unintended innate immune reactivity [36]. Besides FH, Siglecs (sialic acid recognizing Ig-like lectins) are considered second class of SPRRs for their ability to recognize sialic acid and sending inhibitory signals to innate immune cells. In concert with this observation, Siglec-G deficient mouse displayed overly activated response to DAMPs and PAMPs [37] and mouse eosinophils with deficient Siglec-F gave a hyperactive response [38]. Abundance and dominance of PAMPs and DAMPs indicate that there will most likely be more examples of SAMPs and SPRRs that are evolving to maintain self-glycan recognition.

3. Autoinflammatory diseases

The prevalence of a large group of autoimmune diseases is estimated 3–5% of the general population [39, 40]. The immunological deficiencies are fundamentally driven by a broad spectrum of genes and dysfunctional proteins that are not only limited to NLRs. According to the current literature, immune system encompasses perplex and highly specific interactions between numerous different cell types and molecules. Numerous events must occur prior to a cell-mediated or a humoral immune response is activated, which make these series of events vulnerable to disruptions at several stages by number of factors. Therefore, a broad definition of immune system would be “vast communication network of cells and chemical signals distributed in blood and tissue throughout the human body, which regulates normal growth and development of the organism while protecting against disease”.

Immunology emerged from the field of microbiology; hence, generations of immunologists were trained by microbiologists and historically, research in both these fields has addressed the relationship between host and microbe [41]. More than a century ago, Metchnikoff postulated that the primary task of the immune system is not attacking non-self but rather “co-existing with self” or even generation of a multi-cellular organism, despite the internal inconsistencies of its components. When functioning properly, the immune system detects numerous external threats including viruses, bacteria, parasites and stress as well as internal threats, such as tissue injuries, reactive oxygen species (ROS), uric acid crystals distinguishes them from the body’s own healthy tissue. Hence, the deregulation of the immune system may result in autoimmune diseases, inflammatory diseases and cancer. In humans, immunodeficiency can result from a genetic disease such as severe combined immunodeficiency (SCID) or can be an acquired condition such as acquired immunodeficiency deficiency syndrome (AIDS), or else the use of immunosuppressive medication can cause immunodeficiencies. The

other end of the spectrum includes autoinflammatory and autoimmune conditions. Michael F. McDermott coined the term “autoinflammatory” at the end of the twentieth century to explain a group of genetic disorders identified by ambiguous, repeated episodes of fever and abnormal chronic inflammation which generally affect skin, eyes, joints, and gut [42]. In autoinflammatory diseases, the innate immune system is the main player, whereas in autoimmune diseases the adaptive immunity is suggested to be the main effector [43]. However, a growing body of evidence shows that this comparison seems to be an over simplification of the differences. A broader and more accurate definition suggested by Wekell and his colleagues is that *“autoinflammatory diseases are defined by abnormally increased inflammation, driven by dysregulation of molecules and cells of the innate immune system with a host predisposition as necessary and sufficient criteria, frequently associated with activation of the adaptive immune system and potentially with immune dysfunctions such as susceptibility to infections, autoimmunity or uncontrolled hyper inflammation”* [44]. The host’s genetic background is critical in severe inflammation, immune system-mediated tissue damage and even in recurrent episodes of fever. New genes and proteins have been identified and the list of autoinflammatory diseases is continually growing. Mutations in inflammasome-related proteins, especially in NOD-like receptor (NLR) genes, have been reported to be significantly associated with autoinflammatory diseases. Autoinflammatory diseases would be classified into monogenic and polygenic diseases depending on the genes involved [45]. The examples of monogenic autoinflammatory diseases with inflammasome-related proteins and/or NLR gene associations are Familial Mediterranean Fever (FMF), cryopyrin-associated periodic syndrome (CAPS), familial cold auto-inflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), Neonatal onset multisystemic inflammatory disorder (NOMID), NALP12-associated periodic fever, Blau’s syndrome and Crohn’s disease is an example of a polygenic autoinflammatory disease with a NLR association [45, 46]. Therapeutic approaches to treat autoinflammatory diseases include glucocorticoids and non-steroid anti-inflammatory drugs such as colchicine chloroquine, cyclophosphamide, azathioprine, methotrexate, and more recently mycophenolate mofetil. Especially, IL-1 targeting drugs are effective for many of these diseases [47]. The examples of the IL-1 drugs are anakinra, rilonacept and canakinumab. Lastly, the exploration of the multiple steps in the upstream of IL-1 β release reveals a number of potential targets at different steps in the pathway. These drugs could be very effective at blocking several common inflammasome-mediated disorders but may not be used in the treatment of autoinflammatory disorders due to mutations in the inflammasome pathway resulting in hyperactive or constitutive activation that is independent of upstream effectors.

4. Autoimmune diseases

Autoimmunity can be result of a hyperactive immune response, fighting against healthy tissues by losing the ability to distinguish the foreign from self. Autoimmune diseases are a large group of at least 80 chronic disorders in which the immune system mounts an immune response against self-tissues and cells [48]. The concept of autoimmunity goes back to the early twentieth century. Paul Ehrlich initially proposed this concept of *horror autotoxicus*,

meaning that a “normal” body does not generate an immune response against its own tissues. In retrospect, Ehrlich was proven wrong, as the presence of autoantibodies and autoreactivity has become clear [49, 50]. Theoretically, autoimmunity is considered as a deficiency of B or T cell selection, with abnormal cell responses to self-antigens [45, 51]. Autoimmune diseases are regulated by a combination of host genes and environmental factors. Both these can contribute to the predisposition to autoimmunity by altering the sensitivity and behavior of the immune system cells. Therefore, it is reasonable to argue that antigen specificity, recognition, expression, as well as the state and the response of the target tissues are influential in the occurrence of autoimmune diseases [48]. There are many ways to classify the autoimmune diseases. However, the most definitive and helpful way to group them would be according to the target tissue or organs that are damaged by the immune system. A few examples of these autoimmune diseases are listed: (*) NLR-associated diseases)

1. Organ-specific autoimmune diseases: Liver (autoimmune chronic active hepatitis [52]), muscle (myasthenia gravis [53]), blood (autoimmune hemolytic anemia*, autoimmune leukopenia [54, 55]), Gastrointestinal (Crohn’s disease* (IBD-C)), food protein intolerance enteropathies (such as gluten sensitive enteropathy celiac disease* [27]), atrophic gastritis of autoimmune type [56] which leads to pernicious anemia [57], Nervous system (multiple sclerosis*, amyotrophic lateral sclerosis [58]), kidney (immune complex glomerulonephritis [59], skin (vitiligo* [60]).
2. Endocrine organ-specific autoimmune diseases: Adrenal gland (Addison’s disease [27]), ovaries (premature ovarian failure [61]), thyroid gland (Hashimoto’s autoimmune thyroiditis [62]), Graves’ disease [63], pancreas (Type I diabetes* [64]).
3. Systemic autoimmune diseases (the “lupus group”): Lupus erythematosus*, rheumatoid arthritis* [27]).
4. Other autoimmune diseases: Wegener’s granulomatosis, spontaneous male infertility [65].

In *organ-specific autoimmune diseases*, almost any organ in the body can be the specific target for immune response because of the antigen expressed only in that organ. Likewise, in *endocrine organ-specific autoimmune diseases*, immune system directs its response at the organs that are part of the endocrine system. However, in *systemic autoimmune diseases*, such as systemic lupus erythematosus (SLE), immune response targets antigens broadly expressed throughout the body including the central nervous system, kidneys, and heart. The sera from SLE patients contain antibodies directed against various components in the nuclei of cells, including small nuclear ribonucleoproteins (snRNPs); proteins of the chromosomes’ centromeres; and, most markedly, double-stranded DNA. Of all the autoimmune disease categories we discuss in this chapter, there are notable commonalities at each end of the spectrum. As such, thyroid autoantibodies are observed at high frequency in pernicious anemia patients who suffer from stomach autoimmunity. These individuals have a higher prevalence of thyroid autoimmunity than the healthy individuals. The group of rheumatologic diseases also display remarkable common features at the other end of the spectrum. Characteristics of rheumatoid arthritis have a number of resemblances with the clinical features of SLE. In these diseases, immune

complexes are accumulated consistently in the kidneys, joints, and skin. Finally, *other autoimmune diseases* include the diseases that do not belong to any of the aforementioned groups. This is by no means an entire listing of autoimmune diseases, and whether some diseases are completely or partly autoimmune is controversial. Most of these diseases are either a result of serum antibody increase in host, immune-complex deposition in host tissues, high frequency of tissue eosinophils, or elevated infiltration of lymphocytes to target tissues. Because of these immune reactions that take place in host, target tissues are injured in way that may or may not be preventable and moreover may or may not be reversible. Currently used therapies involve glucocorticoids and non-steroid anti-inflammatory drugs. Chloroquine, cyclophosphamide, azathioprine, methotrexate, as well as mycophenolate mofetil, anti-TNF agents (anti-TNF monoclonal antibody), and anti-inflammatory cytokines such as IL-10 and TGF-beta are listed as autoimmune disease treatment approaches [66].

5. Autoinflammatory mechanisms in autoimmune diseases

Approximately 500-million-year-old adaptive immune system recognizes “non-self” substances through the immunoglobulins that are produced by plasma cells and/or T cell receptor interactions with major histocompatibility complex (MHC)/peptide complexes. Cells of the more ancient innate immune system carry receptors that recognize foreign glycans, certain motifs from pathogens [67]. The adaptive immune system is signaled into action by the innate immune system for the optimal host defense [68], therefore it is reasonable to consider the involvement of autoinflammatory mechanisms in autoimmune diseases. By and large, in autoinflammatory diseases, tissue and organ destructions are mediated by cytokine production by macrophages and granulocytes such as neutrophils, whereas in the pathogenesis of autoimmune diseases, tissue and organ damage is mediated by hyper-activation of T and B lymphocytes, and the production of autoantibodies. However, the innate immune system has an effect on the differentiation of immune cells of the adaptive system. The inflammasome-driven innate cytokines Interleukine-1beta (IL-1 β) and IL-18 play roles in the differentiation of T helper subsets Th1 or Th17 by the upregulation of receptors like the IL-2 receptor, expands the lifespan of T cells, and also augmentation of B cell proliferation and antibody production. In the classical autoimmune disease systemic lupus erythematosus (SLE), autoinflammatory reactions have roles in a subset of SLE patients. TREX1 endonuclease gene mutations leads to an increase in the levels of cytosolic DNA which is then recognized by toll-like receptor 7 (TLR7) and TLR9, resulting in the expression of interferon-alpha (IFN- α) [69, 70]. IFN- α enhances the dendritic cell (DC) maturation and activation which causes the subsequent activation of B cells and antibody production [41]. Most recent studies underlie the control of adaptive immunity by innate immune responses that activated DCs have been shown to favor the Th17 cell differentiation from naive T helper cells through the activation of NLRP3 inflammasome complex [71]. Our understanding of immune deficiencies that share the prefix “auto-” resulting from dysfunctional NLRs and inflammasomes has broadened considerably over the past decade. In the next section, NLRs and inflammasomes will be discussed in detail due to their involvement in the progression of autoinflammatory and autoimmune diseases.

6. NLRs in autoinflammatory diseases

Numerous autoinflammatory diseases have been strongly linked with gain-of-function mutations or variations in inflammasome-forming NLRs (NLRP1, NLRP3, NLRP6, NLRP7, NLRP12, NLRC4, and NAIPs) and non-inflammasome-forming NLRs (NOD1/2, NLRP10, NLRX1, NLRC5, and CIITA) [72]. Here, we are going to examine NLR proteins individually for the autoinflammatory diseases in which they are involved.

1. NLRA subfamily:

- a. Class II transactivator (CIITA): CIITA is a human gene which encodes class II, major histocompatibility complex (MHC), transactivator. MHC CIITA was discovered in 1993 as the gene associated with hereditary major histocompatibility complex Class II deficiency, also mutations in CIITA gene were found to be responsible for the bare lymphocyte syndrome in which the immune system is highly compromised and cannot effectively mount a counterattack against the infection [73]. Mainly lymphocytes, dendritic cells, macrophages, and other professional antigen presenting cells are known to express CIITA. To date, a number of autoimmune diseases *but not* autoinflammatory diseases have been reported to be linked to CIITA gene. Later in this chapter, we will revisit the CIITA involvement in the development of autoimmune diseases.

2. NLRPB subfamily:

- a. Neuronal apoptosis inhibitory protein (NAIPs): The first discovered inhibitor of apoptosis protein (IAP) in mammals was NAIP. Mutations and deletions of the NAIP gene have been associated with the spinal muscular atrophy (SMA) phenotype [74]. Like CIITA protein, NAIP was speculated to be involved in autoimmune reactions rather than autoinflammation. In mice different paralogues of NAIP determine the specificity of the NLRC4 inflammasome assembly for distinct bacterial ligands. Innate immune recognition of bacterial ligands by NAIPs determines inflammasome specificity, therefore NAIP has important contributions to the inflammatory reactions. Yet, the involvement of NAIPs in autoinflammation requires further research.

3. NLRC/X subfamily:

- a. NOD1/2: NOD1 and NOD2 are the protein products of CARD4 and CARD15 genes, respectively. The studies focusing on NOD1 and NOD2 primarily involves their signaling activities. The peptidoglycan components diaminopimelic acid (DAP) and muramyl dipeptide (MDP) from Gram-negative and Gram-positive bacteria are recognized by NODs [75]. NOD1 and NOD2 have been associated in a multitude of inflammatory diseases. Especially mutations and SNPs in CARD15 have been associated with Blau Syndrome which is characterized by arthritis, uveitis, and skin rash [76, 77]. It is plausible to suggest that a gain of function mutation of NOD2 in Blau's syndrome is leads to a continuous pro-inflammatory state. Patients are treated with oral steroids and immunosuppressive drugs such as cyclosporine, methotrexate with variable results [46, 78].

- b. NLRC3, 5, and NLRX1: Although, they are listed in this subfamily, their associations or their functional contributions to the pathogenesis of autoinflammatory diseases have not been reported yet. NLRC5, as one of the newest additions to the NLR family; NLRX1 as a unique NLR in that it carries an N-terminal mitochondrial targeting sequence [79], are known to be involved in inflammatory processes and the latter enhances the reactive oxygen species (ROS) production. However, their effect on human health and diseases remains to be elusive.
- c. NLRC4: Interestingly, a de novo gain-of-function mutation in NLRC4 was found to co-segregate with a disease. The disease is characterized by neonatal onset enterocolitis, periodic fever, and fatal or near-fatal episodes of autoinflammation. Over activating mutation in NLRC4 leads to the constitutive production of IL-1 β and macrophage cell death through pyroptosis. These results suggested a novel role for NLRC4 inflammasome in causing a debilitating but treatable autoinflammatory disease [80].

4. NLRP subfamily:

- a. NLRP1: The NLRP1 protein has a distinct structure as compared to other NLRs. Human NLRP1 has a PYD on the N terminus and a CARD on the C-terminus, with ZU5 and UPA domains in the internal region which is attributed to proteolytic activity [81]. Most recently, it was demonstrated that cytosolic double-stranded (ds) DNA triggered the activation of caspase-5 in keratinocytes and subsequent release of IL-1 β . Moreover, interleukin-17A enhanced caspase-5 function through priming of NLRP1-inflammasome. In the study, anti-inflammatory vitamin D have been shown to prevent the IL-1 β release and to suppress caspase-5 in keratinocytes and in psoriatic skin lesions. The NLRP1-dependent caspase-5 activity in psoriasis was suggested by exploring potential therapeutic targets in Th17-mediated skin autoinflammation [82]. Furthermore, another group has recently demonstrated that human NLRP1 is involved in a novel autoinflammatory disorder that researchers propose to call NAIAD for NLRP1-associated autoinflammation with arthritis and dyskeratosis. This disease could be a novel autoimmuno-inflammatory disease having both autoinflammatory and autoimmune characteristics [83].
- b. NLRP3: Among all the NLRs, NLRP3 by far the most studied inflammasome. It is mostly expressed in the cells of innate immunity such as splenic neutrophils, macrophages, monocytes, and dendritic cells [84]. NLRP3 has been linked to autoinflammatory diseases by several research groups. Gain-of-function mutations in the NLRP3 inflammasome lead to the increased production of IL-1 β and cause (CAPS) [85]. CAPS are a large arsenal of diseases classified as familial cold auto-inflammatory syndrome (FCAS), Muckle-Wells syndrome (MW) and neonatal onset multisystem inflammatory disorder (NOMID). These three CAPS are distinguished from one another based on their phenotypic severity. These diseases are basically identified by inflammation affecting skin, joints, eyes, bone, muscles, and central nervous system as a result of increased IL-1 β production. There have been over 50 different NLRP3 mutations identified and suppression of IL-1 β by anakinra, rilonacept, or canakinumab help mitigate clinical symptoms [27]. IgA nephropathy is another disease which is characterized by leukocyte and lymphocyte infiltration in the glomerulus. It is demonstrated that NLRP3 inflammasome localization to mitochondria in tubular epithelium has a crucial role in the progress of this pathology [86].

- c. NLRP12: NLRP12 gene mutations have been found in a group of patients with clinical manifestations identifiable with CAPS, such as recurrent fever and cold sensitivity associated with added symptoms such as neuronal hearing loss, lymphadenopathy, abdominal pain, and acute phase response. These patients did not have mutations at the NLRP3 locus [87].

7. NLRs in autoimmune diseases

To date, many genes have been reported to operate in the development of autoimmunity and modification of inflammation of specific tissues; however, we will continue to focus on the NLR family members that are significantly associated with autoimmune diseases. As discussed in the previous section, it is essential to note that there are overlapping NLRs in the development of both autoinflammatory and autoimmune diseases.

1. NLRA subfamily:

- a. CIITA: Genome-wide association studies (GWAS) and whole exome sequencing studies have found SNPs in CIITA that are linked to celiac disease [88], which is characterized by destruction of the lining of the small intestine by T cells reactive to certain dietary molecules [27]; rheumatoid arthritis which is caused by chronic inflammation of the synovial membrane in the joints [89]; multiple sclerosis (MS) in which autoreactive T cell infiltration in central nervous system results in the destruction of myelin sheaths covering the nerve cells [90]; SLE, a disease where immune response (autoantibodies) against self-antigens affect multiple organs and tissues [91], and type-1 diabetes which is characterized by infiltration of T cells to the pancreatic islets resulting in the destruction of β cells that are responsible for insulin production [92]. Despite the presence of several studies on the association of CIITA gene to a variety of autoimmune diseases, these results were not always reproducible. These variations among the studies were suggested to be related to the age-dependent variation in CIITA gene [92, 93].

2. NLRB subfamily:

- a. NAIP: It is a critical component of the NLRC4 inflammasome and important for the detection of bacterial components, as well as the scaffolding of the NAIP-NLRC4 inflammasome. The expression of the IAP family of anti-apoptotic protein encoding genes in peripheral blood samples and brain tissues from MS patients suggest a role for differential regulation of these proteins in the pathology of MS. As a member of IAP family, NAIP mRNA was found to increase in whole blood [94].

3. NLRC/X subfamily:

- a. NOD1/2: The most common mutation of NOD2 is a frameshift mutation in the LRR region of the receptor that causes the Crohn's disease [88]. The disease is caused by autoreactive T cells against intestinal flora antigens, while the mutations conferring susceptibility to Blau syndrome were reported in the NOD region of the same receptor [76].
- b. NLRC3 and NLRX1: Despite the absence of reports on the association of NLRC3 and NLRX1, there are studies that focused on these 2 NLRs in the context of SLE. The

mitochondrial anti-viral signaling protein (MAVS) is required for anti-viral defense of innate immunity. Melanoma differentiation-associated protein 5 (MDA5) is a retinoic acid inducible gene-I (RIG-I) receptor that recognizes viral dsRNA and undergoes a conformational change which then induces the activation of MAVS, resulting in the type I interferon production [95]. A considerable fraction of patients who suffer from SLE display MAVS aggregation in their peripheral blood cells and that the type-I interferon production contributes to the SLE development. It has been suggested that NLRC3 plays inhibitory roles during inflammation and it may interact with the RIGI-MAVS pathway through stimulator of interferon genes (STING) [96]. Thus, the authors compared and found the same levels of NLRC3 and NLRX1 in the aggregates-positive and aggregates-negative groups of SLE patients, suggesting no involvement of NLRC3 and NLRX1 in SLE development [97].

4. NLRP subfamily:

- a. NLRP1: GWAS and candidate gene analysis studies provided data regarding the association of *NLRP1* variants with vitiligo alone and vitiligo-associated multiple autoimmune diseases. This disease is characterized by the absence of melanocytes in the epidermis which is observed as white patches on the skin. Mutations of NLRP1 were detected in the promoter and/or coding regions of NLRP1 [98]. The functional role of SNPs in NLRP1 is not clear, so the processes linking NLRP1 variations and vitiligo remains unclear. However, the expression of NLRP11 in T cells and Langerhans cells suggest a role for NLRP1 in skin autoimmunity [99]. In addition to vitiligo, NLRP11's involvement in other autoimmune diseases has been noted, including Addison's disease that is characterized by destruction of adrenal cortex and type-1 diabetes [100], celiac disease [101], autoimmune thyroid disorders (aka Hashimoto's Thyroiditis) results from the destruction of thyroid tissue that leads to hypothyroidism [62, 102], systemic lupus erythematosus (SLE), and rheumatoid arthritis [103].
- b. NLRP3: Given the abundance of studies conducted to decipher the roles of NLRP3, more evidence-based report is available for the associations of NLRP3 both in autoinflammatory and autoimmune diseases. SNPs in the NLRP3 gene have been linked to a wide variety of autoimmune diseases among which are type-1 diabetes and celiac disease [104], psoriasis [105].
- c. NLRP2, 9, 11: SNP array analysis in 50 patients with systemic Juvenile Idiopathic Arthritis (s-JIA) showed many disease-related copy number variations (CNVs). Notably, most of them were inherited from either of normal-phenotype parents. In one patient, authors were able to identify two de novo micro-duplications at 19q13.42. The duplications span NLRP2, NLRP9, and NLRP11, also IL-11 and HSPBP1, all of which function in inflammatory pathways. These genes have been suggested be involved in the pathogenesis of s-JIA11 [106].

8. Concluding remarks and future perspectives

Our understanding of how NLRs drive autoimmunity has advanced tremendously in the last decade. Even so, many questions remain unaddressed, mainly because a plethora of different parameters are responsible for the predisposition to autoimmune diseases and the precipitation of such illnesses. In this chapter, we discussed the subject of autoimmunity with respect to NLRs in an attempt to clarify their connection to autoimmunity. The molecular genetics of inflammasomes have been intensively studied in both autoinflammatory and autoimmune diseases and these studies identified mutations in genes encoding NLRs or polymorphisms that cause the development of such diseases. With the advent of new technologies such as genome-wide screening and next generation sequencing, we can now evaluate the pathogenesis of autoinflammation-related diseases from a more holistic point of view. The potency of NLRs in mounting an immune response is crucial for the host, but can also be the reason for life-threatening health problems when inappropriate responses occur. Ever increasing new data from large scale studies deepen our current knowledge on the roles of NLRs, however the function of several of the NLRs remains unclear. In particular, a long-standing question is how NLRs interact with a variety of structurally different ligands. Furthermore, the presence of layers of regulatory pathways and different binding partners make it even more perplexing. Our hope and expectations are that discovery of the complete portfolio of hidden cellular activities that NLRs mediate will tell us how these innate immune molecules function to regulate immunity and will ultimately lead to new, more effective life-saving therapeutic drugs for treatment of autoinflammatory and autoimmune diseases.

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