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Review

From periphery to center stage: 50 years of advancements in innate immunity

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SUMMARY

Over the past 50 years in the field of immunology, something of a Copernican revolution has happened. For a long time, immunologists were mainly concerned with what is termed adaptive immunity, which involves the exquisitely specific activities of lymphocytes. But the other arm of immunity, so-called "innate immunity," had been neglected. To celebrate *Cell*'s 50th anniversary, we have put together a review of the processes and components of innate immunity and trace the seminal contributions leading to the modern state of this field. Innate immunity has joined adaptive immunity in the center of interest for all those who study the body's defenses, as well as homeostasis and pathology. We are now entering the era where therapeutic targeting of innate immune receptors and downstream signals hold substantial promise for infectious and inflammatory diseases and cancer.

INTRODUCTION

The term "innate" is defined as something you are born with, but in the context of immunity, it has been used to denote the part of the immune system that is present from the start of an organism's life and that doesn't undergo genetic rearrangement in the course of an infection. Historically, this contrasts with the term "adaptive immunity," which involves the processes conducted by the specialized immune cells that do undergo genetic rearrangement to "adapt" and address threats to the body, known as lymphocytes. In adaptive immunity, the immune system responds to the invading pathogen by allowing clones of lymphocytes called B and T cells to expand, such that there are more of them present after the infection. This is also how vaccines work by driving the expansion of antigen-specific T and B cells in a controlled and safe way, leaving the immune system ready for a rapid response should an infection occur later. The term "immunity" itself refers to this capacity for adaptation, coming from the Latin word "*immunis*," meaning "exempt" from further infection.

We now know that the body's defense to pathogens involves many cells and factors in addition to lymphocytes, and these have generally been grouped under the term "innate immunity." However, the so-called innate processes can generate a distinct type of memory in myeloid cells that is largely epigenetic.[1] This has been called "trained immunity" to distinguish myeloid cell memory from bona fide lymphocyte memory (see Box 1). This has required us to recognize that all white blood cells, known generally as leukocytes, hold roles in immune responses, with lymphocytes conducting adaptive immunity and myeloid cells conducting innate immunity. The seeming oversimplification of terms reflects the fact that back in 1974, the component parts of innate immunity seemed crude and unspecialized. Unlike the specificity that was becoming apparent in antibodies and then T cell receptors, innate immune factors were much broader in their protective effects and not specific to one pathogen or antigen. They involved such things as the barrier function of skin and epithelia at mucosal sites (which keep many types of microbes from penetrating tissues) and such substances as mucus to trap invading organisms, lysozyme in fluids to break down bacteria, and the acidity of the stomach. The most sophisticated component of innate immunity on the radar in the 1970s was complement, a series of proteins activated in response to bacteria or an antigen/antibody complex, which leads to the lysis of bacteria.

While complement has roots dating back to the very beginning of the field of innate immunity, there has been a resurgence of interest in recent years. There are three distinct pathways of the complement system: the classical, alternative, and lectin pathways. The components of the complement system are produced by the liver and are involved in the detection of blood-borne pathogens, activation of inflammation, and clearance (reviewed in Trouw and Daha[4] and West et al.[5]). Recently, the description of the so-called "complosome" has put a spotlight back on the basic functions of the complement system. The complosome represents intracellular components of the complement system that are involved in basically all physiological processes inside cells of the immune system, including metabolism, cell survival, and gene regulation.[6] For example, cell-intrinsic expression of C3 and C5 in monocytes and macrophages is involved in the production of interleukin (IL)-1β.[7,8] Just in the past year, there have been two studies published in *Cell*, providing new insights into this system. The first study by Desai et al. shows how the C5a component of complement plays critical roles in driving

Box 1. Innate immune memory

Innate immune memory is a phenomenon in which the innate immune system appears to hold a type of limited memory for a defined period of time. Unlike adaptive immune memory, which typically can last for the lifetime of the organism, innate memory lasts more on the order of months to a year (reviewed here[2,3]). Different stimuli, for example, β-glucans and LPS induce different programs of training in myeloid cells, which are induced through epigenetic changes rather than gene recombination observed in adaptive immune cells. The concept of trained immunity goes some ways to explaining how vaccines like bacillus Calmette-Guérin (BCG), which is designed against tuberculosis, can provide broader coverage to a host against a range of infectious microbes, including viruses. The BCG vaccine has been shown to provide protection against lethal candidiasis in severe combined immunodeficient (SCID) mice that lack an adaptive immune system, highlighting the importance of this type of memory occurring within the innate arm of the immune system.[2] Many studies indicate that monocytes and macrophages play key roles in driving the training in mouse studies, with training occurring in progenitor cells in the bone marrow, resulting in central training in addition to cells circulating out in the periphery. The cells' 3D architecture, epigenetic reprogramming including H3K4me1 marks at enhancers, H3K4me3 marks at promoters, and induced expression of lncRNAs are all believed to contribute to the processes of training. Altered metabolism also plays a role, with an increase in aerobic glycolysis present during training with β-glucans. Different ligands induce different metabolites, with glucans inducing fumarate and LPS inducing succinate. Each can influence the overall signals induced during training. Many things can influence training, from diet to environmental and pathological exposure. Much work remains to be done at unraveling the exact molecular mechanisms governing training in order to be able to gain clinically impactful insights into harnessing these pathways for therapeutic benefit.

phagocyte survival and effector functions during fungal infections.[9] The second study by Wu et al. implicates complement as a key regulator of gut health. They show that cells of the gut locally produce complement component C3, which provides protection against invading microbes while saving commensal microbes and ensuring a healthy gut.[10] The complement system was discovered over a century ago, and we are still only learning about its regulatory properties. This work emphasizes the importance of evaluating, reassessing, and putting into context the bigger picture of what we know and appreciating what we still have to learn about the complexities of the innate immune system.

Back in the early days of innate immunity, biologists interested in inflammation began revealing other complex components and processes beyond the complement system. The role of the neutrophil in host defense had been defined, including a description of the respiratory burst driven by nicotinamind adenine dinucleotide phosphate (NADPH) oxidase leading to bactericidal hydrogen peroxide production.[11] From the 1980s on, a large number of intercellular messenger molecules called cytokines were described, including the proinflammatory cytokines IL-1 and tumor necrosis factor (TNF),[12] which were shown to drive a profound increase in inflammatory gene expression in target cells via such transcription factors as nuclear factor (NF)-κB.[13] Cytokines were shown to induce and control physiological processes such as fever and vasodilation, as well as processes like leukocyte adhesion and migration. Cytokine names are generally descriptive, with the name IL signifying *inter* for "between" and *leukin* referring to leukocyte, followed by a number to designate each messenger. Chemokines, which are chemotactic cytokines that attract immune cells to sites of infection, are named in a similarly standardized and numbered way. Importantly, cytokines were found to be a key link from innate immune cells such as macrophages and dendritic cells to adaptive cells, with the messages from myeloid cells driving both the differentiation and anti-pathogen effector functions of particular subsets of T cells.[14]

A true "innate immunity revolution" began circa 1989 when Charles Janeway hypothesized the existence of what he termed "pattern recognition receptors" (PRRs), defined as receptor proteins that recognize "pathogen-associated molecular patterns" (PAMPs), essentially a system by which the host organism's proteins can detect classes of molecules that are not usually present and thus indicative of an infection.[15] The terms PRR and PAMP are now firmly embedded in the immunology lexicon and refer to a large variety of host receptors and pathogen-associated factors (see Table 1). In the article he wrote in 1989, Janeway used the phrase "approaching the asymptote," in which he said if immunologists only concerned themselves with adaptive immunity, their knowledge of the immune system would reach an asymptote or limit. This acted as something of a rallying cry for immunologists, many of whom moved into innate immunity, seeking PRRs and how they might work. Janeway also stated that immunologists had no idea how adjuvants worked, the "dirty little secret" needed for vaccines to elicit their effects. It had been known for decades that simply injecting an antigenic protein into an animal to raise an antibody didn't provoke a strong immune response. Things like complete Freund's adjuvant (heat-killed mycobacteria in paraffin oil) or alum (aluminum hydroxide) needed to be combined with the antigen to garner a strong response, and no one knew why. The identification of PRRs and PAMPs began to clarify how microbial components in adjuvants could stimulate immune responses. But how did non-microbial adjuvants such as alum have similar effects?

The answer involves the idea promoted by pioneering innate immunologist Polly Matzinger, who posited that what the immune system actually responds to is danger.[45] This was a revolutionary and somewhat controversial departure from the traditional view that the immune system exists entirely to discriminate "self" from "non-self." PRRs turned out to be danger sensors, with "danger" in the form of microbial products (i.e., PAMPs) or the products of damaged tissue, which inflammation biologists had been studying for decades. These came to be called danger/damage-associated molecular patterns (DAMPs), and today PAMPs, DAMPs, and other similar classes of molecules that serve as ligands for innate immune receptors represent a central concept in immunity.

By the 1990s, therefore, the scene was set for a major advance in immunology with the description of multiple PRRs, starting with the Toll-like receptors (TLRs),[46,47] which in turn led to the discovery of NOD-like receptors (NLRs),[48–51] C-type lectin receptors (CLRs),[52] RIG-I-like receptors (RLRs),[53,54] AIM2-like receptors (ALRs),[55] and cyclic GMP-AMP (cGAMP) synthase

Table 1. Families of pathogen recognition receptors

Receptor	Localization	Ligand	Function	References
C-type lectin receptors				
Dectin 1 and 2	cell surface	B-glucan and a-Mannan	recognition of unique components in fungi	Takeuchi and Akira[16]
Mincle	cell surface	spliceosome associated protein 130 (SAP130) and Malassezia (fungi)	SAP130 is a component of U2 snRNP released from necrotic cells and activates Mincle	Takeuchi and Akira[16] and Yamasaki et al.[17]
DC-SIGN	cell surface	mannose oligosaccharides or fucose-containing Lewis-type antigens	functions as a PRR against microbes in addition to functioning as a cell adhesion receptor	Gupta and Gupta[18]
Inflammasomes				
AIM2	cytosol	dsDNA	activate IL-1 and IL-18 release downstream following recognition of DNA and cleave gasdermins	Barnett et al.[19]
Caspase-4, -5, and -11	cytosol	LPS and oxidized 1-palmiitoyl-2-arachidonoyl-snglyero-3-phosphorylcholine (oxPAPC)	activate IL-1 and IL-18 release and cleave gasdermins	Barnett et al.[19]
NLRP1	cytosol	*Bacillus anthracis* lethal factor and viral dsRNA	activate IL-1 and IL-18 release and cleave gasdermins	Bauernfeind et al.[20] and Boyden and Dietrich[21]
NLRP3	cytosol	ion flux, organelle dysfunction, and nucleic acids	activate IL-1 and IL-18 release and cleave gasdermins	Barnett et al.,[19] Moretti and Blander,[22] Swanson et al.,[23] and Sharma and Kanneganti[24]
NLRP6	cytosol	lipoteichoic acid (LTA) and viral RNA	activate IL-1 and IL-18 release and cleave gasdermins	Barnett et al.[19] and Wang et al.[25]
Pyrin	cytosol	responds to inactivation of RhoA GTPase	activate IL-1 and IL-18 release and cleave gasdermins	Richards et al.[26] and The International FMF Consortium[27]
Nucleic acid sensors				
cGAS	cytosol and nucleus	dsDNA	recognizes the B-form of DNA via its sugar phosphate backbone	Sun et al.[28]
(2′-5′)-oligoadenylate synthase (OAS)	cytosol	viral dsRNA	binds and cleaves viral dsRNA and induces cell death in infected cells	Schwartz and Conn[29]
Double-stranded RNA-dependent protein kinase (PKR)	cytosol	dsRNA	inactivates the eukaryotic translation initiation factor 2a (eIF2a), blocking viral and cellular protein production; PKR also leads to IFN production and cell death	Clemens and Elia[30]
RIG-I	cytosol	5′-triphosphorylated RNA and short-chain dsRNA	recognizes unique structure on viral RNA	Takeuchi and Akira[16]
IFI16	cytosol and nucleus	DNA	responds to DNA and induces IFNs	Unterholzner et al.[31]

(*Continued on next page*)

Table 1. *Continued*

Receptor	Localization	Ligand	Function	References
MDA-5	cytosol	long cytosolic double-stranded RNA	activates type 1 IFNs	–
NOD-like receptors				
NOD1	cytosol	D-gamma-Glu-mDAP (iE-DAP)	gram-negative bacteria and gram-positive bacteria	Takeuchi and Akira[16]
NOD2	cytosol	muramyl dipeptide (MDP)	gram-negative and gram-positive bacteria	Takeuchi and Akira[16]
Toll-like receptors				
TLR2/6	cell surface membrane	bacterial lipoprotein (Pam2CSK4), lipoteichoic acid, arabinomannan, zymosan, and pore protein	recognizes a range of ligands from bacteria, fungi, and mycobacterium	Takeuchi and Akira[16]
TLR3	endosome	dsRNA (polyI:C)	recognizes and responds to viral-derived double-stranded RNA	Alexopoulou et al.[32]
TLR4	cell surface membrane and endosome	lipopolysaccharide (LPS)	recognition of LPS from gram negative bacteria	Takeuchi and Akira[16]
TLR5	cell surface membrane	flagellin	recognition of bacterial flagellin	Hayashi et al.[33]
TLR7	endosome	ssRNA	viral nucleic acid recognition	Heil et al.,[34] Diebold et al.,[35] and Lund et al.[36]
TLR8	endosome	ssRNA	viral nucleic acid recognition	Heil et al.[34]
TLR9	endosome	unmethylated CpG	can distinguish between self and nonself through recognition of unmethylated CpG, as self CpGs are typically methylated	Hemmi et al.[37]
TLR10 (human only)	cell surface membrane	Gp41 protein from HIV	inhibits MyD88 and activates production of IL-1Rα	Fore et al.[38] and Henrick et al.[39]
TLR11 (mouse only)	cell surface membrane	component of uropathogenic bacteria	expressed in macrophages and liver, kidney, and bladder epithelial cells where it activates NF-κB in response to uropathogenic bacteria	Zhang et al.[40]
TLR12 (mouse only)	cell surface membrane	bind profilin in combination with TLR11	induces IL-12 and IFN-α in response to profilin in plasmacytoid DCs	Koblansky et al.[41]
TLR13 (mouse only)	cell surface membrane	bacterial 23S ribosomal RNA	23S rRNA activates TLR13, leading to the production of IL-1b and other proinflammatory cytokines	Oldenburg et al.,[42] Li and Chen,[43] and Hidmark et al.[44]

(cGAS),[28] among others[56] (Figures 1 and 2). Some were shown to drive multiple antimicrobial processes against bacteria, viruses, fungi, and parasites, including promoting the all-important process of antigen presentation by myeloid cells to lymphocytes, thus providing the link between "non-specific" and "specific" branches of the immune response.

Although transient activation of these signaling cascades is critical for protection against infection, any persistent activation of these pathways can be detrimental and is associated with autoimmune and autoinflammatory conditions. The advances made in understanding the molecular and cellular players of immunology have in turn led to substantial clinical advances, notably in the targeting of cytokines in a range of autoimmune and autoinflammatory diseases, with many millions of patients benefiting in common diseases such as rheumatoid arthritis, inflammatory bowel disease, psoriasis, and atopic dermatitis.[57]

In this review, we describe the main features of innate immunity uncovered in the past 50 years, with a general audience in

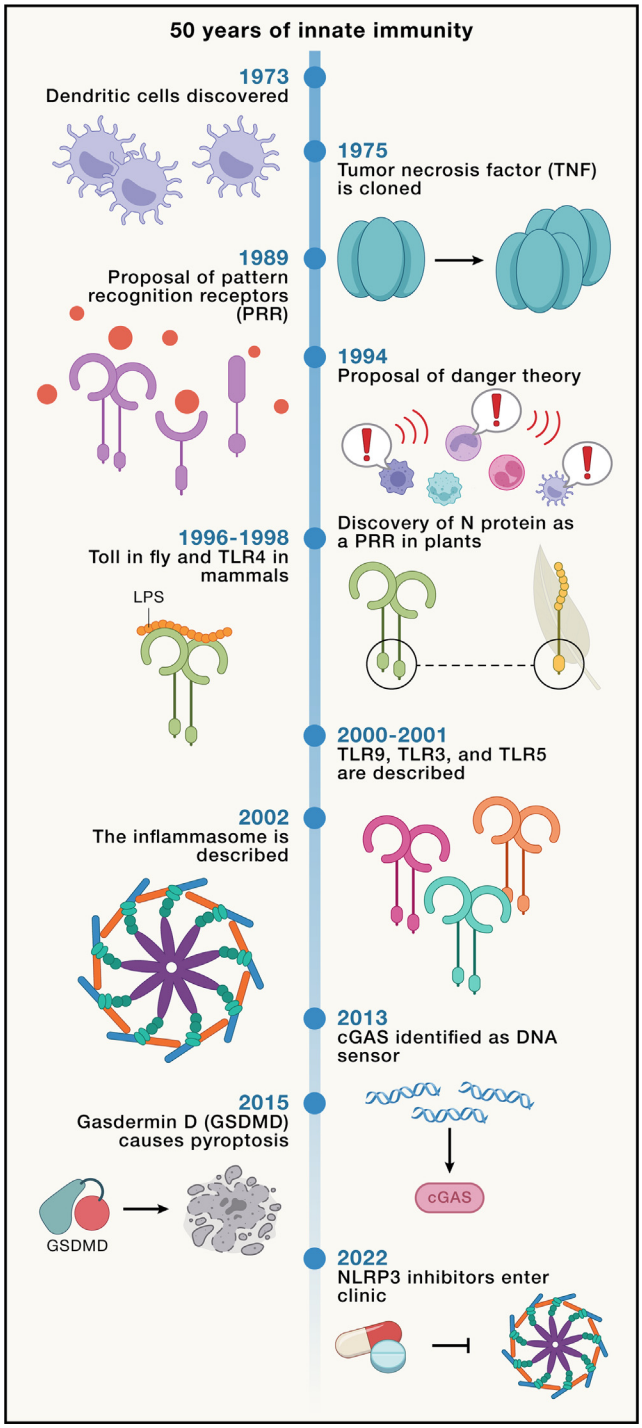

Figure 1. Key discoveries in innate immunity over the past 50 years
Here, we outline the key discoveries in innate immunity through the decades. It begins with the discovery of dendritic cells in 1973 and moves through the key events of cloning cytokines (TNF); identification of the receptors (TLRs, inflammasome, and cGAS); and mechanisms of action to the final development of drugs targeting the pathways (NLRP3 inhibitors).

mind. Many of the pioneering studies were published in *Cell*. We also speculate on whether the targeting of these processes will lead to further therapeutic advances. In many ways, this field is still in its infancy, and we have a lot to learn about the intricacies of regulation within these pathways, particularly epigenetic regulation. Extra components critical to innate immunity might yet be discovered, and we have yet to modulate the power of innate immunity for vaccine development and more effective therapeutics for infectious and autoimmune diseases.

FAMILIES OF PRRs

PRRs are encoded within the genome, differentiating them from the lymphocyte receptors that undergo somatic recombination. These germline-encoded receptors recognize conserved components critical and unique to microbes, such as components of bacterial and fungal cell walls, allowing for discrimination between self and categories of pathogens, as well as cell damage. A catalog of PRR families is outlined in Table 1. Once these receptors become activated, they initiate complex signaling pathways that result in the production of proinflammatory cytokines and antiviral genes.[58] These signals also trigger dendritic cell maturation, induce co-stimulatory molecules, and increase antigen presentation. This enables the innate immune system to directly activate and shape the downstream adaptive immune responses.[15] PRRs are expressed in various subcellular locations and thus transmit information on whether a stimulus comes from the cell surface, within intracellular compartments, within the cytosol, or the nucleus. They can also be secreted into bodily fluids and serve intercellular functions.[59] Cells of the innate immune system such as macrophages and dendritic cells undergo dramatic changes as a result of activation of their PRRs, and non-myeloid cells, such as epithelial and endothelial cells, are increasingly understood to respond to PAMPs and DAMPs in ways that relate to host defense.[60,61] Cells expressing PRRs mature and produce cytokines; they are involved in phagocytosis and trigger a plethora of cell death pathways, impacting other arms of the immune response including opsonization, complement activation, and adaptive immune activation. See Box 2 for a description of the evolutionary diversity of innate immune responses. Here, we will focus on 3 broad categories of PRRs, which cover the breath of recognition from the cell surface to the cytosol and which brought great insight into innate immunity in the past 50 years.

TLRs

TLRs are type 1 transmembrane glycoproteins and are structurally characterized by the extracellular leucine-rich repeat (LRR) motifs required for ligand binding and the intracellular cytoplasmic Toll-IL-1 receptor (IL-1R)-resistance (TIR) homology domain required for downstream signaling.[16] To date, there are 10 TLRs identified in the human genome (TLR1–10) and 13 in mice (TLR1–13), although TLR10 is not functional in the mouse due to the presence of a stop codon in the sequence. Each TLR is triggered by unique PAMPs, as outlined in Table 1. TLRs1, 2, 4, and 5 are localized to the cell surface, while TLR3, 7, 8, and 9, which all play roles in nucleic acid sensing, are found on intracellular compartments.[16]

In order to begin to describe the discovery of this family of receptors in humans and mice, we first have to cover the early

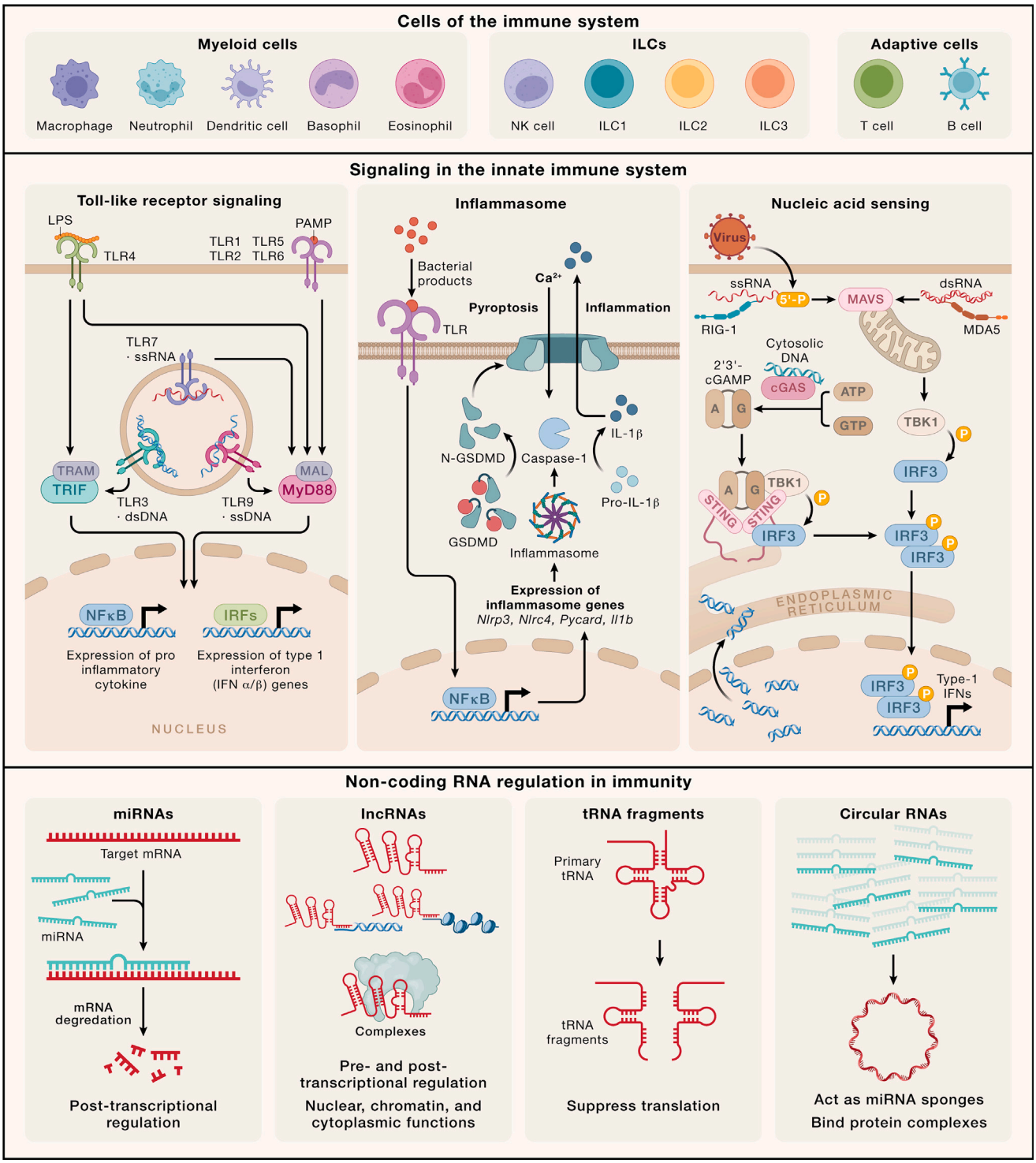

Figure 2. Molecular patterns induce a variety of cellular responses via distinct sensing pathways

TLR signaling: plasma membrane-bound or endosomally localized TLRs signal through adaptors and kinases situated in the cytosol to drive inflammatory cytokines and type 1 interferon (IFN) responses. Inflammasome: the inflammasome is a multiprotein complex formed in the cytosol in response to microbial ligands or host danger signals. Activation leads to caspase-1 activity, cleavage, and release of IL-1β or IL-18. Nucleic acid sensing: DNA is recognized by cGAS within the cytosol, leading to the production of the second messenger cGAMP, which signals through STING to induce type 1 IFNs. RNA is sensed by RIG-I or MDA-5 to induce type I IFNs. Noncoding regulation: many families of noncoding RNAs including lncRNAs, tRNA fragments, miRNAs, and circRNAs have emerged as key regulators of biological processes including transcription, splicing, and translation, which can impact immunity.

Box 2. Evolutionary diversity of innate immunity

Comparing innate immune processes across animal species has revealed some interesting similarities and differences that continue to provide insights into the evolutionary diversity of innate immunity. The sea urchin has a huge repertoire of innate receptors, including 222 TLRs and 203 NLRs. Its signaling repertoire is equally expansive, with 58 TIR adapter-like proteins, 36 TRAF proteins, and 541 death-domain-containing proteins.[219] This is likely because the sea urchin lacks adaptive immunity and so has an expanded innate repertoire to ensure adequate diversity to deal with infectious microbes that might infect it. The same can be said of plants, with, for example, *Arabidopsis* having hundreds of TLRs and NLRs.[220] The cGAMP/STING pathway turns out to be conserved even in bacteria, where it provides defense against bacteriophages.[221,222] Bats have a different NLRP3 with an altered LRR domain, leading to a less active NLRP3 inflammasome. This might be one of the reasons why bats can tolerate viruses that are otherwise pathogenic in humans.[219] Finally, horses have TLR4 that can recognize a type of LPS from *Rhodobacter sphaeroides*, which infects horses. That type of LPS is an antagonist against human TLR4. This allows horses to mount an appropriate immune response to that particular bacterium.[219]

work on the IL-1R type 1 (IL-1R1) and the initial discovery of the protein Toll in the fruit fly *Drosophila*. A number of labs in the 1980s characterized the functions of the pleiotropic proinflammatory cytokine IL-1 as a critical regulator of T cell activation, an inducer of fever in addition to the acute phase response, which involves induction of proteins such as C-reactive protein in the liver.[62] The gene encoding the receptor for IL-1, IL-1R1, was first cloned in 1988, but curiously, the predicted sequence did not contain any recognizable motifs to indicate its mechanism of action.[63] That was until 1991, when the protein Toll in *D. melanogaster* was shown to have a homologous cytosolic domain to the IL-1R (now termed the TIR domain).[64] Toll was first identified as being involved in dorso-ventral polarity in the fly (reviewed in Belvin and Anderson[65]). Interestingly, a pattern we have seen emerge over time is that proteins have a "double job" and can play crucial roles in developmental processes in addition to processes within the immune system, at least in *Drosophila*. The *Drosophila* Toll receptor binds to the ligand Spätzle, signaling through an adaptor protein called Tube, resulting in activation of the kinase Pelle and subsequent activation of the NF-κB transcription factor family member Dorsal, which is inhibited by the protein Cactus. Meanwhile, in 1994, Barbara Baker and colleagues reported on N protein in tobacco plants, which conferred resistance to tobacco mosaic virus. It was Barbara Baker who coined the term "TIR" domain, given the homology between Toll; IL-1R1; and N protein, a disease-resistance protein.[66] All these signaling components were then found to have homologs within the mammalian system. When loss-of-function mutants for Toll were generated in the fly, researchers were surprised to find these flies were highly susceptible to fungal infections yet resistant to gram-negative bacterial infections.[67] It was found that activation of the Toll pathway by fungal infection induced the production of the antimicrobial peptide drosomycin downstream of the NF-κB family member *Drosophila* immunity factor (DIF), while diptericin is the antimicrobial peptide produced in flies in response to gram-negative infection, which signals through the immune deficient (IMD) pathway.[68–71]

Bioinformatic analysis revealed more mammalian proteins with TIR domains, leading to the description of the TLR family, which all have TIR domains but, unlike IL-1R1, which has immunoglobulin domains, have LRRs. TLR4 was the first to be identified as a mammalian homolog of Toll. Medzhitov et al. were the first to show that an active form of TLR4 was capable of inducing the expression of the co-stimulatory molecule B7 (cluster of differentiation 80 [CD80]), a critical finding as it provided a link to T cell activation from an innate immune receptor.[46] Following this work, genetic mouse models identified TLR4 as the critical receptor responsible for the gram-negative bacterial product and driver of sepsis lipopolysaccharide (LPS).[47,72] In the 1960s, a spontaneous mutation had occurred in the C3H/HeJ mouse colony at the Jackson Laboratory, rendering the mice resistant to LPS toxicity. It was the work of the Beutler lab that traced the missense mutation to exon 3 of the TLR4 gene (previously referred to as the *Lpsd* gene).[47] Jules Hoffmann and Bruce Beutler were awarded the Nobel Prize in medicine in 2011 for their work on uncovering Toll as an innate sensor in flies and TLR4 as the receptor for LPS in mice, respectively.[47,67] In 1999, the Akira lab developed TLR4-deficient or knockout (KO) mice and showed they failed to respond to LPS, again confirming that indeed TLR4 is the signaling receptor for LPS.[73] One important aspect, however, in LPS lethality was the discovery that LPS could induce caspase-11 and promote a type of cell death called pyroptosis via caspase-1 (discussed further below).[74] LPS was then shown to bind caspase-11 and activate this process, which in fact was key to LPS lethality.[75,76] Importantly, low-dose polyI:C was able to bypass the requirement of TLR4 for LPS lethality in mice. The main effect of TLR4, therefore, in mice with regard to lethality is to induce caspase-11, which mediates the effect of LPS.

TLR signaling

TLR family members signal through similar intersecting pathways, and because TLR4 represents the best-studied family member, it will be our focus here. TLR4 is made up of LRR sequences on the extracellular N terminus and the TIR signaling domain that lies inside the cell membrane and forms the platform for downstream signaling cascades. It does not operate alone in the recognition of LPS, but instead, it works with a number of co-receptors, including LPS-binding protein (LBP), which binds to LPS in micelles, allowing another co-receptor CD14, to interact (reviewed in Pålsson-McDermott and O'Neill[77]). CD14 increases the sensitivity to LPS by over 1,000-fold[78] and forms a complex with MD2 and TLR4 on the cell surface. 5 out of the 6 lipid chains within LPS are buried within the hydrophobic pocket of MD2, which bridges the dimerized complex together to form the "m" structure, solved by crystallography in 2009 by Park et al.[79] These conformational changes that occur once LPS is bound initiate the downstream signaling cascade inside the cell (reviewed here[80]). TLR4 has the most complicated downstream signaling of all the TLRs as it has the ability to interact with multiple adaptor proteins. In 1997, myeloid differentiation primary-response protein 88 (MyD88) was shown to signal downstream of IL-1R1 to activate NF-κB.[81,82] It has a TIR domain and signals

through homotypic interaction with the TIR domains in TLRs.[77] In the case of TLR4 signaling, MyD88 functions alongside the adaptor protein MyD88 adaptor-like (MAL; also known as TIR-domain-containing protein, TIRAP) to drive NF-κB.[83,84] MyD88 also contains a death domain, which mediates its interactions with IL-1R-activated kinase-4 (IRAK4), which then activates IRAK1 and 2 through autophosphorylation.[80,85,86] TNF receptor-associated factor 6 (TRAF6) is a ubiquitin ligase recruited to the complex and initiates the formation of K63 ubiquitin chains, forming scaffolds for the recruitment of transforming growth factor (TGF)B-activated kinase 1 (TAK1) and TAK-binding proteins (TAB2 and 3).[87] Next, the nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha (IκBα) kinase complex is activated through phosphorylation and undergoes K48-linked ubiquitination and degradation, releasing NF-κB to translocate to the nucleus and activate proinflammatory genes.[80,88] Although most TLRs use a similar MyD88-dependent signaling pathway, TLR4 is unique in that it also engages in parallel with the adaptor proteins TIR domain-containing adapter-inducing interferon (IFN)-β (TRIF) and TRIF-related adaptor molecule (TRAM).[89–91] Downstream signals include TRAF3, which recruits inhibitor of nuclear factor kappa-B kinase subunit epsilon-IKKε/TANK-binding kinase (TBK1), which then phosphorylates and activates IFN regulatory factor 3 (IRF3). This in turn moves to the nucleus, where it induces the production of antiviral proteins, including type I IFNs.[91–93] These higher-order complexes that form downstream of the adaptor protein engagements are sometimes referred to as the "Myddosome" and "Triffosome" complexes, which act as supramolecular organizing centers (SMOCs), promoting these signaling events.[87] While MyD88 signaling occurs at the plasma membrane, activation of the Triffosome requires endocytosis of the receptor complex and subsequent activation from the endosomal compartment of the cell.[93]

TLR4 activation has been shown to drive profound metabolic changes in macrophages, enhancing glycolysis and promoting what is termed the "Warburg effect," meaning a shift to aerobic glycolysis and a change in mitochondrial metabolism.[94] This is critical for the macrophage response to LPS since inhibiting glycolysis decreases production of the key proinflammatory cytokine IL-1β.[94] This process requires dimerization of the glycolytic enzyme pyruvate kinase isozyme M2 (PKM2), which translocates to the nucleus, promoting the expression of HIF-1alpha-dependent genes, including those encoding enzymes in glycolysis but also IL-1β itself.[95] Profound metabolic rewiring occurs in the LPS-activated macrophages with the accumulation of the Krebs cycle intermediate succinate.[94] This in turn has been shown to be oxidized by the Krebs cycle enzyme succinate dehydrogenase (SDH), leading to reverse electron transport through complex I in the mitochondria, driving the production of reactive oxygen species (ROS), and further promoting hypoxia-inducible factor 1 alpha (HIF-1α) activation.[96] LPS has also been shown to increase fumarate production via repression of the Krebs cycle enzyme fumarate hydratase.[97] This disturbs the mitochondria via an increase in mitochondrial membrane potential, leading to the release of mitochondrial double-stranded RNA (dsRNA), which is detected by the RNA sensorsretinoic acid-inducible gene-I (RIG-I) and melanoma differentiation-associated protein 5 (MDA-5), promoting the expression of IFN-β. Finally, LPS has also been shown to increase expression of the enzyme aconitate decarboxylase-1, encoded by the gene *Irg-1*. This converts aconitate to itaconate, which has a wide range of anti-inflammatory effects, acting to limit inflammatory macrophages.[98] These studies contributed to the field of immunometabolism, which began to emerge in earnest from 2013 (reviewed in Day and O'Neill[99] and Peace et al.[100]). Further work is needed on the complexities of immunometabolism in innate immunity. A whole multitude of metabolites are changing dynamically, and we are only at the start of the effort to determine their roles in the regulation of immune cell effector functions.

All of these discoveries happened over a roughly 20-year period and are a triumph of molecular immunology. While many of us in the field were still scratching our heads as we considered the emerging complexities of TLRs, other PRRs entered the picture and further widened the view.

DISCOVERY OF THE INFLAMMASOME

The second area within innate immunity that has seen a frenzy of activity over the past 20 years or so concerns inflammasomes. "Inflammasome" is a term for a multiprotein complex involving one of several PRRs that forms in the cytosol and plays critical roles in the activation of the cytokines IL-1β and IL-18, as well as processing gasdermin family proteins that mediate an inflammatory type of cell death called pyroptosis. The NLR sensors that comprise the inflammasome respond to PAMPs and DAMPs.[101] Here, we provide a brief overview of this field, and for a more in-depth account, we direct you to the following reviews.[19,102] Each known PRR-associated inflammasome and its activation are outlined in Table 1. One of the dominant PRR families is the nucleotide-binding domain (NBD), LRR-containing (NLR) protein family. These come in two flavors: those containing a pyrin domain (PYD) in the N terminus, referred to as NLRPs, or those containing a CARD domain (CYD) in the N terminus, referred to as NLRCs. Activation of the inflammasomes leads to proteolytic cleavage of pro-caspase-1 into its catalytically activated form. Caspase-1 processes the pro forms of IL-1β and IL-18 into their active forms, which are released through pores formed in the cell by gasdermin D.[103,104] Formation of the gasdermin D pore also causes a specialized form of cell death referred to as pyroptosis, which is associated with inflammation and downstream activation of adaptive immune cells[19,102] (Figure 2). There are a number of additional gasdermin family members, all of which show specific cell and tissue expression patterns with emerging roles in human health and disease. All gasdermins form pores, but the exact mechanisms driving their activation remain under investigation (reviewed in Broz et al.[105]).

NLRP3 inflammasome

NLRP3 represents the best studied of the inflammasomes, with a wide array of activating processes including ion fluxes (K^+ efflux and Ca^{2+} flux); metabolic changes (mitochondria and lysosome dysfunction, fatty acid synthesis, and hyperosmotic stress); and even nucleic acids (dsDNA, viral RNA, and oxidized

DNA).[22–24] How so many varying molecules can activate a single sensor is unclear and continues to be a focus of intense research. Activation of the NLRP3 inflammasome occurs in two steps. Step 1 involves upregulation of the components of the pathway, typically through activation of NF-κB, and signal 2 involves direct activation of the downstream sensor.[20,106] The requirement for priming differs between cell types and specific inflammasomes. While NLRP3 is advantageous to the host in responding to bacterial and viral infections and a range of noxious stimuli, it is worth noting that excessive activation of this pathway has been associated with a number of inflammatory conditions, including cryopyrin-associated periodic fever syndrome (CAPS) which are heritable and involve activating mutations in NLRP3.[107]

NUCLEIC ACID SENSING, UNCOVERED

Another perhaps unexpected development in innate immunity was the uncovering of sensors of DNA, which provoke innate immunity. DNA therefore moved from not only being the information molecule of life but also a key driver of immunity and inflammation, particularly if it showed up in the wrong place outside the nucleus. Or, to use the phrase of a central figure in the field of innate immunity, Vishva Dixit, if it "breached the sanctity of the cytosol." In fact, back in 1928 even before DNA was shown to be the genetic material scientist Frederick Griffith famously showed a "transforming principle" activating the immune system, which later turned out to be DNA.[108] The reason we do not respond to our own DNA is that it is encased within the protective walls of the nucleus or mitochondria and is therefore hidden from PRRs. We now know this process is error prone, and escape of self-DNA into the cytosol is associated with autoimmune conditions such as systemic lupus erythematosus (SLE). From the mid-2000s, there was a major push to identify and characterize the main players involved in the direct sensing of DNA within the cytoplasm. TLR9, which is localized to endosomes, was shown to be a receptor for CpG DNA, common in bacteria.[37] Absent in melanoma 2 (AIM2) was identified as a DNA sensor capable of binding directly to DNA and inducing the formation of an inflammasome leading to IL-1 and IL-18 release.[55,109] However, less was known about how DNA was sensed to lead to the production of type 1 IFNs. A number of potential DNA receptors were shown to play some role including IFI16, DEAD-box helicases (so called after the motif D-E-A-D [asp-glu-ala-asp]) and HNRNPA2B1.[110] From early studies, it was clear that STING played a key role in this pathway and, at first, was considered to not only be the adaptor but potentially the direct sensor. However, the field made rapid progress with the discovery of cyclic dinucleotides and the important role for the adaptor stimulator of interferon genes (STING) in regulating this pathway.[28,111,112]

cGAS is a cytosolic DNA sensor that activates type I IFNs through production of the second messenger cGAMP, which activates the adaptor STING[28] (for a thorough review of the field, please read the following[113,114]). cGAS is present in the cytosol under physiological conditions in an autoinhibited state. Once cGAS binds DNA, it undergoes conformational changes leading to the production of cGAMP from the cell's stores of ATP and GTP.[28] cGAMP then functions as a second messenger to bind and activate STING. STING had been known to bind and respond to bacterial second messengers, but cGAMP was the first example of a host-derived second messenger activating this pathway.[111] STING activates the kinase TBK1, which phosphorylates the transcription factor IRF3, leading to its translocation to the nucleus and subsequent activation of type 1 IFNs. STING can also activate NF-κB, leading to the production of proinflammatory cytokines.

The main receptors that recognize RNA within the cytosol are RIG-I and MDA-5 (Figure 2; Table 1). These cytosolically localized receptors are important in the recognition of single-stranded RNA (ssRNA) and dsRNA, respectively.[53,54] Interestingly, our own RNA contains modifications, including adenosine to inosine changes (A to I edits), which helps protect our own RNA from activating these receptors.[115] These receptors play key roles in protection against viral RNA infections, including influenza, hepatitis, and West Nile virus (reviewed in Kato and Fujita[116]). RIG-I can recognize key structures in RNA, including 5′ppp-, while MDA-5 favors long dsRNA. When the receptors are activated, they result in the robust induction of type I IFNs (Figure 2).

HOW ACTIVATION OF THE INNATE IMMUNE PATHWAYS CONTROLS ADAPTIVE IMMUNITY

For many immunologists, the most important feature of innate immunity was how it promotes adaptive immunity, and the discovery of that connection is perhaps the most critical finding in immunology over the past 50 years. The 2nd half of the 2011 Nobel Prize for Medicine was awarded to Dr. Ralph Steinman for his discovery, almost exactly 50 years ago, of dendritic cells.[117] Dendritic cells (DCs) are often referred to as professional antigen-presenting cells, as they are instrumental in capturing antigens from tissue sites throughout the body and presenting them to T cells within the immune system's specialized lymph nodes. Dendritic cells reside in the periphery and express high levels of innate immune PRRs. Once activated, dendritic cells undergo maturation involving increased expression of proinflammatory cytokines, migratory chemokine receptors, and upregulation of surface proteins that interact with T cells and activate downstream adaptive immune responses. The critical role for the TLR signaling pathway in DC maturation was demonstrated when DCs from MyD88-deficient mice failed to undergo maturation.[118,119] Without that critical adaptor protein used by most TLRs, only stimulation via the alternative TRIF adaptor downstream of TLR4 could activate the antigen presentation activities of DCs. Furthermore, early work from the MyD88-deficient mice highlighted the importance of the TLR signaling pathway for driving inflammatory T cell responses in particular, as less inflammatory T cell subtypes and B cells retained most functions in the absence of the bulk of TLR signaling.[119] Dendritic cells are not a single-cell type, and over the last number of years, many DC subtypes have been characterized, including those that are tissue resident within each organ (reviewed in Iwasaki and Medzhitov[120]). DCs engage with cytotoxic T cells (CTLs) for the removal of viral pathogens and tumors. Intracellular pathogens and protozoa are dealt with by CTLs and Th1 (type 1

subtype) of T cells, while Th17 (type 3 subset) cells play a critical role in control of extracellular pathogens. For a more in-depth discussion of DCs and adaptive immunity, we refer you to the following reviews.[120,121]

DISCOVERY OF THE ILCs

Members of the innate lymphoid family of cells were first described in the mid-1970s, but the nomenclature utilized today was only proposed in 2013.[122] Innate lymphoid cells (ILCs) play key roles in the regulation of the innate immune responses. ILCs act as innate counterparts to T cells, with the functional subtypes of these cells seemingly mirroring the functional subtypes of T cells but without the antigen-specific T cell receptor. The founding members of the ILC family, natural killer (NK) cells, act similarly to CD8 CTLs, while ILC1s are Th1 like, ILC2 are Th2 like, and ILC3 are similar to type 3 responding T cell subtypes (TH17, TH22). NK cells were first named in 1975[123] and shown to be important in early responses to viral infections. ILCs generally function within mucosal tissues, where they are typically present at low numbers and are involved in activation of inflammation, tissue remodeling, metabolic control, and influence on adaptive immune responses. For an in-depth review of the ILC literature, we recommend the following reviews.[122,124]

CONTROLS ON INNATE IMMUNITY

Another very fruitful area in the past 50 years has been the elucidation of multiple controls on innate immune pathways. Transient activation of the complex signaling cascades downstream of PRRs is critical to the maintenance of homeostasis. Therefore, it was important to understand the key players involved in controlling the timing of these immune cascades. Like all aspects of the immune response, there are layers of regulation that contribute to the exquisite timing observed in innate immune cells. The speed of protein turnover is one simple layer of regulation. For example, the transcription factor p65 is retained in the cytoplasm by IκB and only travels to the nucleus following activation of the PRRs. Following stimulation, IκB undergoes phosphorylation and subsequent degradation within the 28S proteasome. However, the turnover of IκB is rapid as it itself is induced by NF-κB, and therefore, once IκB is translated, it resumes its role of retaining p65 within the cytoplasm, contributing to the transient nature of the response.[77]

There have been many processes identified that play roles at various stages of the innate immune response. We have created a summary table outlining some of the key players (Table 2) and will focus on two key controllers here: (1) A20 and ubiquitination and (2) noncoding RNAs, both of which have seen an extensive body of findings in the past 20 years.

A20 and control of ubiquitination

A20 (also known as TNFAIP3) is a universally expressed ubiquitin-modifying protein that is itself induced downstream of NF-κB signaling. A20 is unique in that it can work to add ubiquitin chains or remove them. A20 functions to negatively regulate NF-κB signaling in addition to inhibiting cell death.[186] It became clear that A20 is a critical component for the maintenance of homeostasis following the generation of A20-deficient mice.[187] Although the mice are born at expected Mendelian ratios, they die quickly after birth due to multiorgan inflammation,[187] and the main contributor of the dysregulated signaling appears to stem from the TLR pathway.[188] A20 is strongly associated with a number of inflammatory diseases, such as SLE, due to single-nucleotide polymorphisms (SNPs) identified in the gene.[189] A20 has also been implicated as a tumor suppressor, as SNPs are associated with lymphoma.[186]

Many arms of the innate immune signaling pathways are controlled through the process of ubiquitination. Specific ubiquitin marks determine if a protein is removed or activated. Lysine 48 (K48)-linked ubiquitin chains mark proteins for degradation through the proteasome, while lysine 63 (K63)-linked ubiquitin chains act as activation scaffolds for downstream signaling. A20 mediates negative regulation of the TLR[190] and NOD[191] signaling pathways through deubiquitination of K63-linked proteins and has also been shown to control the NLRP3 inflammasome.[191]

Emerging roles for noncoding RNA in the regulation of innate immunity

Although much of the early work on innate immune signaling focused on protein cascades and cellular phenotypes, the development of next-generation sequencing has opened a Pandora's box of RNA transcripts with apparent regulatory function. The majority of the human genome is actively transcribed, but an important question has been: how much of the RNA transcripts that don't encode proteins are functionally relevant? The most advanced area of understanding as it relates to noncoding RNA in innate immunity is the field of microRNA research. MicroRNAs (miRs) were first identified in the early 1990s,[192,193] and their specific roles in the innate immune system emerged in the late 2000s, with the description of miR155 and miR146a as regulators of NF-κB.[194–196] miRNAs are small RNAs (23 nucleotides in length), transcribed mostly from RNA polymerase II, with a few being RNA polymerase III transcripts. They can be encoded as independent genes or emerge from the introns of protein-coding genes. A primary transcript is transcribed then processed within the nucleus before being exported to the cytoplasm, where it undergoes cleavage by Dicer to form a duplex. One strand of the RNA is then loaded onto the RNA-induced silencing complex (RISC), which then guides the complex to the 3′ untranslated regions (UTRs) or target mRNAs, leading to repression of the target protein.

miR155 and miR146 represent the two best-characterized miRNAs within the innate immune system, and evidence suggests that they can even counterbalance each other. Both miR155 and miR146 are highly inducible following inflammatory activation with TLR ligands or following infection. miR155 is proinflammatory and targets negative regulators SHIP1 and SOCS-1, while miR146 is anti-inflammatory targeting TRAF6 and IRAK1.[194–196] miR146a-deficient mice show symptoms of chronic inflammation and autoimmunity, and these mice express higher levels of miR155, adding evidence that these miRNAs act as counterbalances to the homeostatic inflammatory response. Deficiency of miR155 in mice has wide-ranging impacts on their immune system. They show reduced responses in endotoxic

Table 2. Negative regulators of innate immunity

Protein name	Mode of regulation	Knockout phenotype	SNPs	Reference
A20 binding inhibitor of NF-κB1 (ABIN1)	partner of A20	knockout mice have similar phenotype to A20 KO mice	SNPs associated with SLE and psoriatic arthritis	Nanda et al.,[125] Bowes et al.,[126] and Han et al.[127]
A20	ubiquitin-modifying enzyme deubiquitylates TRAF6	develop autoimmunity	SNPs associated with rheumatoid arthritis, SLE, psoriasis, coeliac disease, Crohn's disease, type 2 diabetes, atherosclerosis, and lymphomas	Mele et al.[128]
Cylindromatosis (CYLD)	inhibits NF-κB activity	KOs are sensitive to chemically induced tumors and impaired fear memory	mutations in CYLD have been identified in patients with polycythemia vera	Sun,[129] Li et al.,[130] and Trang et al.[131]
Deubiquitinating enzyme A (DUBA)	negatively regulates interferons through deubiquitination of TRAF3	mice with DUBA-deficient T cells develop excessive inflammation in the small intestine after challenge with anti-CD3 antibodies	variants associated with X-linked intellectual disability and congenital malformation	Kayagaki et al.[132] and Rutz et al.[133]
IL-10	blocks the induction of proinflammatory cytokines downstream of ligands such as LPS	knockout mice develop colonic inflammation beginning at 3 weeks of age	genome-wide association studies (GWASs) associate IL-10 SNPs with inflammatory conditions and cancer	Berg et al.[134]
IL-1R2	decoy receptor for IL-1 signaling	KO mice show increased susceptibility to collagen-induced arthritis	SNP association in a cohort of Chinese patients with cervical cancer	Supino et al.,[135] Shimizu et al.,[136] and Niu et al.[137]
IRAK-M	expressed in monocytes and macrophages; it is induced by TLRs and negatively regulates the pathway through inhibition of the formation and activation of the IRAK1/4/TRAF6 complex	KO mice show abnormal osteoclast development and increased inflammatory responses to infection	SNPs associated with early onset asthma	Balaci et al.[138] and Kobayashi et al.[139]
LLRC25	inhibits TLRs by promoting autophagic degradation of p65; inhibits IFN by promoting the degradation of RIG-I	–	–	Feng et al.[140] and Du et al.[141]
Metallothionein 3 (MT3)	negative regulates caspase-11 through regulation of zinc levels	KOs show abnormalities in psychological behavior and show accelerated onset and progression of ALS	SNP associations with autism	Chowdhury et al.,[142] Koumura et al.,[143] Koh and Lee,[144] and Yu et al.[145]
MyD88S	Myd88S arises from alterative splicing of the MyD88 gene and behaves as a dominant negative of IIL and LPS signaling	–	–	Janssens et al.[146]
NLRX1	negatively regulates RIG-I signaling by binding MAVS; also negatively regulates TLR signaling by targeting TRAF6 and IKK	KOs produce higher levels of IFN-β and IL-6 following influenza infection; MAVS constitutively interacts with RIG-I in the KO mice	–	Moore et al.,[147] Xia et al.,[148] and Allen et al.[149]

(*Continued on next page*)

Table 2. ***Continued***

Protein name	Mode of regulation	Knockout phenotype	SNPs	Reference
NLRC5	negatively regulates NF-κB by inhibiting IKK phosphorylation; regulates type 1 IFN by blocking RIG-I and MAVS interactions; NLRC5 is also an major histocompatibility complex (MHC) class 1 transactivator	reports of increased TLR signaling and IFN production in KO mice, in addition to the KO mice having impaired CD8T cell responses due to loss of MHC class I	SNPs associated with susceptibility to pulmonary aspergillosis	Tong et al.,[150] Cui et al.,[151] Kumar et al.,[152] Zhong et al.,[153] Meissner et al.,[154] and Biswas et al.[155]
NLRP11	targets TRAF6 for degradation via the ligase RNF19A and is primate specific	–	SNP is associated with susceptibility to Crohn's disease, and a gene duplication was found in juvenile idiopathic arthritis patients	Ellwanger et al.[156] and Wu et al.[157]
Nod2 (Card15)	suppresses NF-κB	KOs show enhanced TH1 cytokines IL-12, IFNy, and IL-18 following stimulation with peptidoglycan	SNPS associated with excessive Th1 responses and Crohn's like disease	Watanabe et al.[158]
Pleckstrin homology-like domain, family A, member 1 (PHLDA1)	negatively regulates TLR4 signaling through interactions with Toll-interacting protein (TOLLIP)	information from mouse genome informatics (MGI) indicates that KOs are viable with no obvious defects in immune function	–	Chowdhury et al.[142]
Pumilio homolog 1 (PUM1)	negatively regulates LGP2; can suppress TLR4 mRNA translation	KO exhibits reduction in body and organ size	deletions associated with *Pumilio1*-associated developmental disability, ataxia, and seizure; PADDAS	Liu et al.,[159] Yoon et al.,[160] Lin et al.,[161] and Gennarino et al.[162]
Radioprotective 105 (RP105)	interacts with TLR4 complex to inhibit interactions with LPS	DCs from RP105 KO mice produced increased cytokines in response to LPS; mice were more susceptible to LPS challenge, producing higher levels of TNF post LPS injection	one SNP in cow is associated with a mycobacterium infection	Divanovic et al.[163] and Casas et al.[164]
Suppressor of cytokine signaling-1 (SOCS-1)	suppresses IRAK1 and inhibits type 1 IFN	KO mice die within 3 weeks due to multi-organ failure; they are more susceptible to endotoxic shock	SNPs associated with rheumatoid arthritis and early onset autoimmunity	Nakagawa et al.,[165] Kinjyo et al.,[166] Lamana et al.,[167] Hadjadj et al.,[168] and Gingras et al.[169]
Soluble suppression of tumorigenicity 2 (sST2)	ST2 is the receptor for IL-33 and the main form of the receptor functions to promote NF-κB signaling, while the soluble version inhibits the signaling; sST2 acts as a decoy receptor and binds IL-33	–	SNPs in the distal promoter, which impact the full gene, are associated with atopic dermatitis	Shimizu et al.,[136] Griesenauer and Paczesny,[170] and Hayakawa et al.[171]

(*Continued on next page*)

Table 2. *Continued*

Protein name	Mode of regulation	Knockout phenotype	SNPs	Reference
Single Ig IL-1-related receptor (SIGIRR or IL-1R8)	interacts with TRAF6 and IRAK; competes for binding to MyD88 and acts as a coreceptor for anti-inflammatory cytokine IL-37	KO mice show enhanced responses to IL-1 and LPS but not TNF and show increased susceptibility to endotoxic shock and colitis	SNPs associated with infectious diseases including tuberculosis	Garlanda et al.,[172] Wald et al.,[173] and Riva et al.[174]
Soluble TLRs (sTLRs)	they block interactions between the TLRs and their agonists	–	–	Liew et al.[175]
Tollip	autophosphorylates IRAK1	IL-13-treated Tollip KO mice show significantly increased lung eosinophilic inflammation	mutations associated with development and/or prognosis of idiopathic pulmonary fibrosis (IPF)	Zhang and Ghosh,[176] Burns et al.,[177] Ito et al.,[178] and Bonella et al.[179]
Triad domain-containing protein 3A (TRIAD3A)	ubiquitylates TLRs	KOs have microglial defects	recessive mutations in *RNF216/TRIAD3* cause Gordon Holmes syndrome (GHS)	López-Gómez et al.[180] and George et al.[181]
TNF-related apoptosis-inducing ligand receptor (TRAILR)	stabilizes IkBa	KOs show enhanced immune responses with increased levels of IL-12, IFN-α, and IFN-γ	SNP is associated with enhanced responses to IFN-β treatment in MS patients	López-Gómez et al.[180] and Diehl et al.[182]
Ubiquitin-specific peptidase 38 (USP38)	through altering ubiquitination through interactions with KDM5B; USP38 also negatively regulates IFN signaling	KO mice are more susceptible to endotoxic shock and acute colitis, producing higher levels of inflammatory genes compared with wild-type mice; KO mice also have increased K33-linked ubiquitination and higher expression of TBK1	SNPs linked to susceptibility to asthma and malaria	Zhao et al.,[183] Lin et al.,[184] and Manjurano et al.[185]

shock models, and their adaptive immune responses are skewed with effects on T and B cell responses during infection or autoimmunity.[197] For more on miRNAs in the innate immune system, we recommend the following comprehensive reviews.[197,198]

Although microRNAs were the first to have an understood regulatory role, the largest group of RNAs produced from the genome are long noncoding RNAs (lncRNAs). Depending on the analysis pipeline, there are predicted to be anywhere between 20,000 and 100,000 lncRNAs, with a small number of these loci being shown to encode small functional peptides.[199] In 2013, a lncRNA named *lincRNA-Cox2* was shown to impact genes of the innate immune system, with downregulation of genes such as IL-6 occurring when *lincRNA-Cox2* was removed, while IFN genes were upregulated.[200] XIST represents the best-studied lncRNA, first identified in 1991.[52] XIST is encoded on the X chromosome and is required for X chromosome inactivation in females. Interestingly, TLR7 is encoded on the X chromosome and is capable of escaping X inactivation.[201] This has been shown to be particularly important in T cells and links this important noncoding RNA with regulation relating to autoimmunity in particular SLE, which disproportionately impacts women as well as individuals with Klinefelter syndrome who carry an extra copy of the X chromosome. Excess TLR7 during this condition could explain some of the signaling defects observed (reviewed in Syrett and Anguera[202]). A recent study showed that simply overexpressing XIST in male mice resulted in the formation of autoantibodies, and T and B cells from these mice resembled those of wild-type females.[203] Over the past decade, this field has greatly expanded, with many publications on lncRNAs and immunity. For in-depth reviews of this field, we recommend the following.[204–206]

THERAPEUTIC POSSIBILITIES

The uncovering of innate immune processes and their regulation was followed by efforts to exploit these remarkable findings for therapeutic gain. New and exciting prospects are emerging.

The immediate application of the identification of PRRs was in vaccine adjuvancy, as it was highly likely that their discovery would explain how Janeway's "dirty little secret" might work in molecular terms. Despite much effort, progress on rationally designing adjuvants for vaccines has been slow and is ongoing.[207,208]

The importance of innate immunity in vaccine adjuvancy was elegantly demonstrated in a study by Bali Pulendran and colleagues,[209] involving the vaccine for yellow fever, comprising a live attenuated virus termed YF-17D. This is one of the most effective vaccines ever developed, providing protection for decades from a single shot. To elicit its effects, it requires a wide array of innate sensors, comprising TLR2, TLR3, TLR7, TLR9, RIG-I, and MDA-5, which are presumably sensing diverse PAMPs in the virus. Separately, detoxified versions of LPS were tested, even before the finding that TLR4 was the receptor for LPS, and monophosphoryl lipid A (MPL) emerged as an adjuvant. It is used in combination with a plant extract termed QS-21 (which is a liposome made from plant saponins from the Chilean soap bark tree) and cholesterol in a vaccine for shingles, as well as in a malaria vaccine. AS04 is an adjuvant comprising aluminum salts with MPL and is used in vaccines for human papilloma virus and hepatitis B virus. A modified form of the TLR9-agonist CpG DNA is used in a vaccine for hepatitis B. Clinical trials are currently running with imiquimod (a small molecule used to treat genital warts and subsequently shown to be a TLR7 ligand) in influenza, flagellin (the TLR5 ligand) in influenza, and a dsRNA polymer (the TLR3 ligand) in influenza and rabies. In addition, there is substantial interest in STING agonists, especially in the context of anti-tumor vaccines but also in influenza, HIV, and tuberculosis.[207,210]

The mRNA vaccines for COVID-19 raised new questions about how innate immune-activating ligands relate to adjuvanticity. The vaccines include modified mRNA encoding the Spike protein from SARS-CoV-2 in a lipid nanoparticle (LNP) comprising ionizable lipids and cholesterol. The LNP itself was shown to have adjuvant properties when used with a protein antigen, while the vaccines were shown to require MDA-5 for their immunogenicity and, intriguingly, not a whole range of other PRRs.[208] Whether MDA-5 is sensing the RNA in the vaccine itself or endogenous RNA, perhaps of mitochondrial origin, is not known.

Although vaccination adjuvants exploit PRR activation to prime the immune system, on the therapeutic flip side of the coin, there are also efforts to block PRRs in autoinflammatory and autoimmune diseases. Antibodies that target TLR2 in such conditions as ischemia reperfusion injury and rheumatoid arthritis showed preclinical promise[211] but have not advanced, largely because of lack of efficacy in human clinical trials. Attempts were also made to target TLR4 in sepsis,[212] with the antagonist Eritoran showing only marginal effects in clinical trials, which could have been because of the timing of the intervention clinically or perhaps because of the need for careful patient stratification.

NLRP3 has proven to be a target of great interest, given its potential role in a wide range of autoinflammatory and autoimmune conditions, most notably in diseases of the CNS such as Alzheimer's disease and Parkinson's disease.[213] A small-molecule inhibitor termed CRID3/MCC950, which was originally shown to block signal 2 for IL-1β production, was then shown to specifically target NLRP3 by binding the nucleoside triphosphatase (NTPase) domain (NACHT domain) essential for ATP-dependent oligomerization during NLRP3 inflammasome activation.[214,215] Multiple compounds based on this inhibitor as well as other NLRP3 inhibitors are at various stages of clinical development, with trials running in CAPS, osteoarthritis, gout, myelodysplastic syndrome, asthma, Parkinson's disease, and coronary artery disease.[216] It may well be that inhibiting NLRP3, or even other inflammasomes, will have therapeutic applicability across multiple inflammatory diseases. It might even be possible that inhibiting NLRP3 will be somewhat akin to antibiotics and infectious diseases—one drug bringing benefits in a number of diseases, in this case, diseases where inflammation driven by myeloid cells is pathogenic.

There is also substantial interest in targeting the cGAS-STING pathway in such conditions as rheumatoid arthritis, stroke, SLE, and neurological disorders.[217,218]

The advent of cytokines led to the development of multiple cytokine-targeting therapeutics, as well as inhibitors of cytokine-driven signals, notably in the Janus kinase (JAK) family of

tyrosine kinases, bringing substantial benefits to patients. Targeting specific cytokines or signals has not been especially problematic in terms of increasing the risk of infection or cancer. The hope is that the targeting of PRRs, or indeed the signals they activate, will bring similar, if not superior, clinical benefits, especially in diseases where targeting cytokines might not be especially effective or is yet to be proven.

CONCLUDING REMARKS

50 years ago, our understanding of innate immunity was primitive, as that is how innate immunity was then viewed. A concerted effort, across many hundreds of laboratories and involving thousands of researchers, from research assistants to graduate students to post-doctoral scientists publishing their work, has revealed a whole world of interconnected processes that are far more sophisticated than the primitive assumptions. Exciting findings will continue to be made and will likely reveal even more component parts in innate immunity. These future findings will further increase our understanding of these essential and most fundamental of biological processes, the targeting of which must hold great therapeutic promise for immune-mediated and inflammatory diseases and cancer.

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DECLARATION OF INTERESTS

S.C. is a paid consultant for NextRNA Therapeutics. L.A.J.O'N. is a paid consultant for Sitryx Therapeutics, Sail Biomedicines, and Montai Health.

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