OPINION

Homeostasis-altering molecular processes as mechanisms of inflammasome activation

Adrian Liston and Seth L. Masters

Abstract | The innate immune system uses a distinct set of germline-encoded pattern recognition receptors (PRRs) to initiate downstream inflammatory cascades. This recognition system is in stark contrast to the adaptive immune system, which relies on highly variable, randomly generated antigen receptors. A key limitation of the innate immune system's reliance on fixed PRRs is its inflexibility in responding to rapidly evolving pathogens. Recent advances in our understanding of inflammasome activation suggest that the innate immune system also has sophisticated mechanisms for responding to pathogens for which there is no fixed PRR. This includes the recognition of debris from dying cells, known as danger-associated molecular patterns (DAMPs), which can directly activate PRRs in a similar manner to pathogen-associated molecular patterns (PAMPs). Distinct from this, emerging data for the inflammasome components NLRP3 (NOD-, LRR- and pyrin domain-containing 3) and pyrin suggest that they do not directly detect molecular patterns, but instead act as signal integrators that are capable of detecting perturbations in cytoplasmic homeostasis, for example, as initiated by infection. Monitoring these perturbations, which we term 'homeostasis-altering molecular processes' (HAMPs), provides potent flexibility in the capacity of the innate immune system to detect evolutionarily novel infections; however, HAMP sensing may also underlie the sterile inflammation that drives chronic inflammatory diseases.

The molecular basis for pathogen recognition fundamentally differs between the innate and adaptive immune systems. Innate recognition of pathogens by mammals is based on a set of 20–40 pattern recognition receptor (PRR) proteins, each of which recognizes a fairly narrow set of pathogen-associated molecular patterns (PAMPs). The PRRs are mainly concentrated within the Toll-like receptor (TLR), C-type lectin receptor (CLR), NOD-like receptor (NLR) and RIG-I-like receptor (RLR) families, and they detect a diverse set of pathogen molecules[1]. In contrast to the adaptive immune system, in which random genomic recombination facilitates the generation of antigen receptors with the collective potential to recognize a diverse range of antigens, the dedication of single genes to single PAMPs (or PAMP clusters) places a sharp evolutionary constraint on the number of PAMPs that can be recognized by the innate immune system.

Evolutionary pressure will select for innate pathogen receptors that recognize only the most prevalent and conserved PAMPs. This system provides effective recognition of opportunistic pathogens, most of which will contain at least one PAMP within the structural range recognized by the innate immune receptors (FIG. 1a). This system compensates for the failure to recognize the more numerous essential, yet poorly conserved, antigens possessed by each pathogen (FIG. 1b). However, the danger of relying on the detection of a limited number of PAMPs is revealed through specialized pathogens, which are often able to bypass the triggering of the innate immune system, either through the loss of PAMPs, through structural modification of PAMPs (FIG. 1a) or through targeted disruption of PRR signalling pathways[2]. Arguably, the main function of the adaptive immune system is to compensate for this theoretical 'blind spot' in innate immunity[3], but there is a growing consensus that the innate immune system includes more sophisticated recognition systems than originally envisioned.

This potentially exposes one of the major limitations of the mechanism of PAMP detection by a discrete set of structures — namely, that this allows the possibility of specialized pathogens evolving to avoid the recognized PAMP structures. One evolved 'work-around' is the system of detecting damage-associated molecular patterns (DAMPs). DAMPs are an alternative system that is still based on a simple molecule recognition model, but the generated DAMP molecules are of self origin; for example, uric acid crystals[4], extracellular ATP[5] and oxidized phospholipids[6]. This concept was originally conceived as a mechanism to allow the innate immune system to detect widespread cellular death without directly detecting pathogen products themselves[7].

In this Opinion article, we make a conceptual distinction between the innate recognition of DAMPs and what we propose to term 'homeostasis-altering molecular processes' (HAMPs). Although both DAMP sensing and HAMP sensing involve the detection of self in a state that is associated with tissue damage, DAMPs use the same recognition principle of PAMPs, whereby a sensor has evolved that recognizes a distinct molecular pattern. By contrast, HAMPs are the read-out of a loss of cellular homeostasis within a live cell, in which the innate immune sensor responds to cellular imbalance rather than to a distinct molecular pattern (TABLE 1). Intracellular inflammasome complexes provide the best examples of this, as we discuss below.

Innate immunity and the inflammasome

Within the cell, multiple PRRs can directly detect invading pathogens. The detection of microbial nucleic acids by retinoic acid-inducible gene I (RIG-I; also known

as DDX58), melanoma differentiation-associated gene 5 (MDA5; also known as IFIH1), cyclic GMP–AMP synthase (cGAS) or absent in melanoma 2 (AIM2), and the detection of bacterial PAMPs by neuronal apoptosis inhibitory protein (NAIP) and nucleotide-binding oligomerization (NOD) receptors, essentially follow the classical model, with direct detection of PAMPs by the specialized receptor resulting in the activation of distinct innate immune response genes. In addition, some of these same receptors can directly engage mislocalized host products that are analogous to their microbial counterparts, such as cGAS-mediated recognition of mitochondrial DNA, which therefore represents innate immune recognition of a DAMP[8].

A diverse set of these intracellular proteins, including AIM2, NLRC4 (NOD-, LRR- and CARD-containing 4), NLRP1 (NOD-, LRR- and pyrin domain-containing 1), NLRP3, NLRP6 and pyrin, feed into a single response pathway, the inflammasome. The inflammasome was initially assumed to follow the classical model, with various PAMP or DAMP molecules binding to their sensor proteins. Indeed, this has proved to be the case for some of these sensors, such as AIM2 (which recognizes DNA) and NAIPs (which sense PAMPs, such as flagellin, and activate NLRC4). However, a more nuanced view is now evolving for the others, in which there is no defined ligand and instead activation is manifested indirectly, allowing the sensor to respond to a more generalized loss of cellular homeostasis.

Although these initial recognition events have proved to be difficult to elucidate, the downstream activation of inflammasomes has been well characterized. Briefly, the sensor proteins oligomerize into a multiprotein complex that contains the adaptor protein ASC and the enzyme caspase 1. This assembly, known as the inflammasome, is able to activate both the production of mature interleukin-1β (IL-1β) and IL-18, and the highly inflammatory pathway of cell death known as pyroptosis[9]. The inflammasome is a key platform-mediating defence strategy against pathogens. Following the triggering of inflammasome assembly, the inflammasome complex itself is a long-lived structure because of the prionoid-like oligomerization of ASC[9]. Indeed, this inflammasome 'speck' can persist outside the cell after pyroptosis, in the circulation or in the peripheral tissues, where it can function as an inflammatory signalling intermediate to bystander cells[10–12]. Inflammasome activation can result in a highly potent local inflammatory environment and strong influxes of neutrophils and natural killer (NK) cells[13]. Elaborate regulation, ensuring selectivity and certainty, is thus a prerequisite for complex formation, as the consequences of inappropriate activation of the inflammasome are considerable and long lasting[13,14].

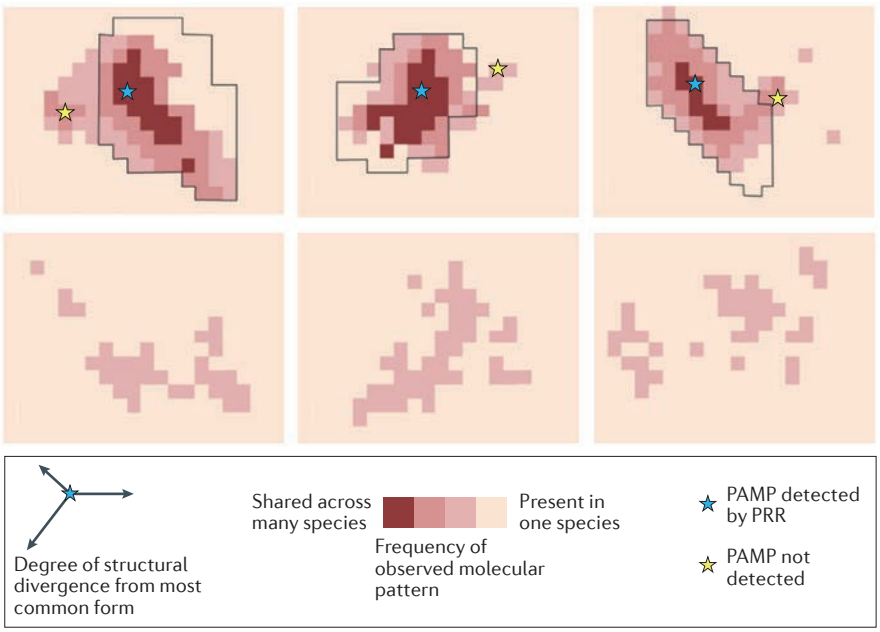

Figure 1 | **Innate immune receptors are limited by structural conservation.** Hypothetical structure conservation maps for six pathogen-associated molecular patterns (PAMPs). Every position on the map represents a structural deviation from the neighbouring positions. The level of conservation is indicated by colour, with red representing highly conserved structures across species. **a** | Three highly conserved PAMPs targeted by pattern recognition receptors (PRRs). The structural diversity recognized by the PRR is boxed. The structure expressed by a typical opportunistic infection is indicated by a blue star; the structure expressed by a specialized infection is indicated by a yellow star. **b** | Three poorly conserved PAMPs that have crucial pathogen functions but are inappropriate for PRR targeting.

HAMPs as inflammasome triggers

Despite the clear function of the inflammasome pathway as an innate sensor–response system for microbial infection, the structural basis by which pathogen recognition occurs has proved elusive. Unlike the classical innate sensor molecules in the TLR, CLR and RLR families, there has been little success in identifying simple PAMP–sensor relationships for the inflammasome pathway. NAIP and AIM2 have a fairly limited set of PAMP activators and seem to act solely through direct ligand binding in exactly the same manner as TLR, CLR and RLR pathogen sensors. However, the model of direct PAMP binding to innate pathogen recognition sensors is insufficient to explain the activity of several inflammasome initiators. Principle among these is NLRP3, which is the prototype for a number of other inflammasome-forming sensors, such as NLRP1, NLRP6 and pyrin.

The broad reactivity of NLRP3, in particular, cannot currently be explained using the classical PAMP–sensor binding model, and it is thought to be highly unlikely that direct structural recognition is involved for each proven trigger ligand. Without necessarily showing direct binding, a range of mediators are capable of activating NLRP3; these range from viral and bacterial products to sterile products such as particulate matter, crystalline self molecules, saturated fatty acids[15], reactive oxygen species (ROS)[16] and damaged mitochondria[17]. Furthermore, the system is not even reliant on the introduction of novel molecular patterns, as disturbances including low potassium levels, reduced fatty acid oxidation[18] and amino acid starvation[19] can trigger NLRP3-dependent inflammasome formation. With such a diverse range of structures and conditions able to activate NLRP3, it is highly unlikely that a direct binding paradigm will suffice. Rather, the simplest model would be one in which NLRP3 is a signal integrator that detects any of a multitude of molecules and conditions that induce altered homeostasis, in the same way that one can detect the ripples in a pond without seeing the initial stone that was

Table 1 | **Comparison of the key features of PAMPs, DAMPs and HAMPs**

Molecular trigger of innate immunity	Source of trigger	Host recognition mechanism	Potential molecular variety in triggers
PAMP	Foreign (for example, bacterial LPS)	Molecular pattern (for example, LPS recognition by TLR4)	Constrained
DAMP	Self (for example, cellular ATP)	Molecular pattern (for example, ATP recognition by P2X7)	Constrained
HAMP	Self (for example, RHOA inactivation)	Molecular process (for example, loss of pyrin phosphorylation)	Broad

DAMP, damage-associated molecular pattern; HAMP, homeostasis-altering molecular pattern; LPS, lipopolysaccharide; P2X7, P2X purinoceptor 7; PAMP, pathogen-associated molecular pattern; RHOA, RAS homologue gene family member A; TLR4, Toll-like receptor 4.

thrown (FIG. 2). It is also possible that a dual-requirement system is in play, with NLRP3 becoming more promiscuous in ligand binding in an 'inflammasome activation-permissive' environment induced by altered homeostasis.

For the inflammasome sensor pyrin, a molecular basis now exists for the HAMP hypothesis. Pyrin is kept in an inactive state by a sensitive molecular pathway in which the small GTPase RAS homologue gene family member A (RHOA) activates serine/threonine protein kinase N1 (PKN1) and PKN2, which in turn phosphorylate pyrin on serine 242 (REF. 20). 14-3-3 proteins (which are a family of conserved proteins involved in many diverse cellular signalling processes) then bind phosphorylated pyrin, locking it into an inactivated state[21] (FIG. 3a). Bacterial toxins such as *Clostridium difficile* toxin B (TcdB) activate pyrin; however, they do not trigger the immune system only as PAMPs because toxin function, rather than structure, is required for pyrin activation. Instead, TcdB-mediated inactivation of RHOA disturbs the phosphorylation pathway, which leads to a loss of pyrin phosphorylation, removal of the 14-3-3 inactivation lock and thus activation of pyrin (FIG. 3b). This mechanism allows pyrin to respond to any microbial stimuli that alter the activity of RHOA, PKN1 and PKN2, or 14-3-3. As such, pyrin can function as a global sensor of considerable cellular alterations in the phosphorylation balance (that is, altered homeostasis), rather than as a reporter for a single PAMP or DAMP. From an evolutionary point of view, this system provides a capacity for functional, rather than structural, detection of pathogen toxins, freeing it from the structural limitations of the classical PAMP detection model. However, the HAMP detection model also has the resulting disadvantage that noninfectious triggers that disturb cellular phosphorylation processes will also result in pyrin activation. For example, individuals with defects in prenylation that lead to the inactivation of RHOA and subsequent pyrin activation develop hyper-IgD syndrome[20,22].

The molecular basis of pyrin-mediated recognition of HAMPs may function as a paradigm for the ability of NLRP1, NLRP3 and NLRP6 to respond to such a diverse range of molecular inputs. The best characterized of these sensors is NLRP3; however, the exact molecular basis of NLRP3 activation remains unknown. One potential mechanism by which NLRP3 functions as a signal integrator for multiple different alterations to self may be by monitoring mitochondrial status. Damaged mitochondria can directly activate NLRP3 (REF. 17), and many of the other cellular disturbances that initiate the NLRP3-dependent inflammasome affect mitochondria. For example, endoplasmic reticulum (ER) stress activates NLRP3 via mitochondrial damage[23], and peptidoglycan sugars from bacteria activate NLRP3 through hexokinase binding and mitochondrial modification[24]. However, until the molecular requirements for NLRP3 activation are identified, the integration point will remain speculative. Indeed, a recent study showed that NLRP3 is phosphorylated, in a similar manner to pyrin, such that NLRP3 activation may also rely on the sensing of phosphorylation[25]. Finally, it is worth noting that IL-1β itself may function as both an effector molecule and a HAMP sensor. IL-1β is produced in an immature (inactive) form that requires cleavage of an amino-terminal pro-domain by the assembled inflammasome. It has recently been found that pro-IL-1β can be cleaved and activated by bacterial proteases as well as by host caspase 1 (REF. 26). Crucially, this pathway of immune activation results in enhanced clearance of the bacteria, but patho-adaptive mutations that prevent the cleavage of IL-1β can arise in invasive bacteria; notably, these mutations do not arise if IL-1β is pharmacologically inhibited during bacterial infection[26]. As this process of innate immune activation relies on the detection of function (protease activity) rather than of structure, it has similarities to the HAMP model that we have discussed above.

The 'guard model' as a paradigm

When considering how the mammalian innate immune system has evolved, it is highly informative to examine immunity in plants, which do not have an adaptive immune system. As proposed by Jones and Dangl[27], it is possible to conceive that initially direct recognition of pathogens (pathogen-triggered immunity (PTI)) was sufficient to mediate survival; however, opportunistic invaders promptly deployed effectors that could prevent this direct detection. In response, plants required a mechanism to detect effectors, which can be accomplished very effectively in an indirect manner. As such, the guard hypothesis

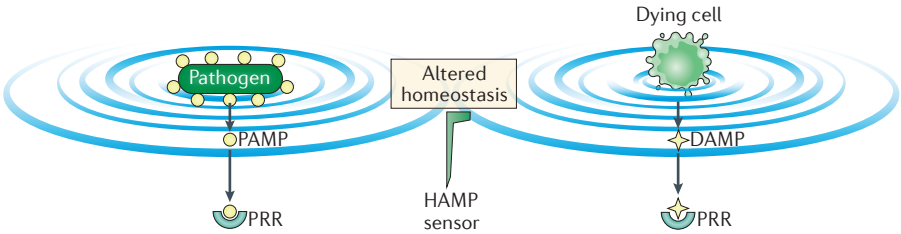

Figure 2 | **Direct and indirect pathways of innate immune sensing.** Homeostasis-altering molecular process (HAMP) monitoring allows indirect recognition of diverse molecular patterns through detection of the effect on cellular processes. Direct recognition of molecular patterns requires specialized receptors. HAMP recognition is not based on direct recognition of the molecular patterns, but rather on the detection of the common effects that each process has on cellular homeostasis. The difference is analogous to detecting an object thrown into a pond. Direct recognition would require the detection of each possible object that could be thrown, but HAMP recognition is based on the detection of the ripples that are generated regardless of the identity of the initial object. DAMP, damage-associated molecular pattern; PAMP, pathogen-associated molecular pattern; PRR, pattern recognition receptor.

states that pathogen-elicited changes in homeostatic parameters function as the basis for innate immune receptor activation. This is accomplished by members of the plant nucleotide-binding site leucine-rich repeat (NBLRR) family of proteins, which have many similarities to the mammalian NLR proteins.

One example of where interesting similarities exist between plants and mammals is in the detection of ROS (FIG. 4). In plants, ROS have been proposed to activate the ADR1 family of NBLRRs[28], to induce sialic acid and downstream triggering of NON-EXPRESSER OF PATHOGENESIS-RELATED GENES 1 (NPR1) and the transcription of defence genes[29], or to induce the triggering of LESION SIMULATING DISEASE1 (LSD1) and cell death[30]. In this respect, activation of plant ADR1 proteins may be similar to mammalian NLRP3 activation by mitochondrial ROS[18]. These links can also be extended because both of these pathways are negatively regulated by autophagy[31,32], have a requirement for K^+ efflux[29,33] and Ca^{2+} accumulation[34,35], and are increasingly sensitive to low temperature[36,37]. Many of these parameters, particularly ROS, can be regulated by mitochondria in both plant[38] and mammalian[17] innate immune pathways, which is perhaps unsurprising given the appropriation of this organelle via the ancestral endosymbiosis of a microorganism. In this way, the metabolic status of mitochondria is a key read-out of HAMPs as an indicator of altered homeostasis.

Another example of where plant and mammalian innate immune recognition mechanisms converge is in the usage of 14-3-3 proteins as the guards of innate activation. We have outlined above how this works in the context of mammalian pyrin activation, with phosphorylation of pyrin maintaining the presence of 14-3-3 bound to the inactive immune sensor. In this regard, it is an indirect version of the guard hypothesis, in which traditionally it would be the 14-3-3 guard protein itself that is targeted. That is certainly the case in plants, in which many different 14-3-3 isoforms are the direct targets of microbial effectors[39]. The result of this can be either modification of the pathogen effector itself, or sequestration and/or interaction with downstream pathways to promote disease resistance[39]. In this way, plant 14-3-3 proteins fulfil the traditional criteria as guard proteins of innate immunity and represent the signalling pathway created by HAMPs as a surrogate marker of infection.

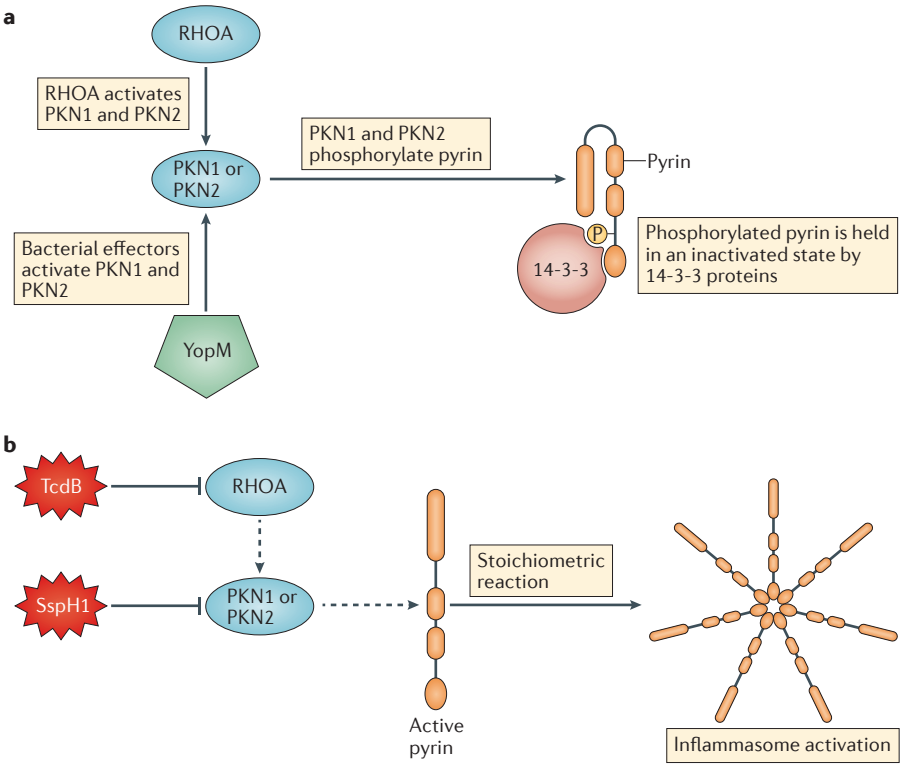

Figure 3 | **Molecular basis for pyrin as a signal integrator for HAMP recognition. a** | The activity of the GTPase RAS homologue gene family member A (RHOA) drives the activation of serine/threonine protein kinase N1 (PKN1) and PKN2, which in turn phosphorylate pyrin on serine 242. Phosphorylated pyrin is bound by 14-3-3 family members, and this binding locks the pool of pyrin present in the cell into an inactive state, preventing inflammasome activation. Bacterial effectors such as YopM can also promote PKN1 and PKN2 activity to subvert pyrin inflammasome activation. **b** | Toxins that inactivate RHOA cause a cascade of events (indicated by dashed arrows) in which pyrin ceases to be phosphorylated, causing 14-3-3 to dissociate and the free pyrin to initiate the formation of the inflammasome. In principle, the pathway would be sensitive to any pathogen-initiated events that impede any point of the phosphorylation cascade, such as degradation of PKN1 by *Salmonella* spp. SspH1, although this has yet to be tested. HAMP, homeostasis-altering molecular process.

Predictions of the HAMP model

The HAMP model for innate pathogen sensors gives rise to several testable predictions on the basis of evolutionary principles, as we discuss below.

Prediction 1. The first prediction is that organisms without an adaptive immune system will have more sophisticated networks for identifying HAMPs. With innate pathogen receptors detecting a limited number of widely expressed PAMPs, the key advantage of the adaptive immune system is to recognize pathogen antigens outside of this limited range. It would therefore be predicted that organisms without an adaptive immune system will be under enhanced evolutionary pressure to develop and refine HAMP detection pathways. The initial identification of the guard mechanism in plants (see above) supports this prediction. However, in the absence of a comprehensive catalogue of HAMP detection pathways, this prediction remains theoretical.

Prediction 2. The second prediction is that specialized pathogens will have evolved counter-regulatory systems to evade HAMP detection pathways. As opposed to opportunistic pathogens, specialized pathogens are under evolutionary pressure to evolve immune evasion processes. Just as specialized pathogens have evolved mechanisms to bypass classical PAMP recognition by innate pathogen receptors (for example, through the loss or masking of PAMPs, or the neutralization of innate pathogen-sensing signalling pathways[40]), they are likely to have evolved mechanisms to avoid detection by HAMP receptors. A comparison of opportunistic and specialized pathogens would be predicted to reveal the mechanisms by which

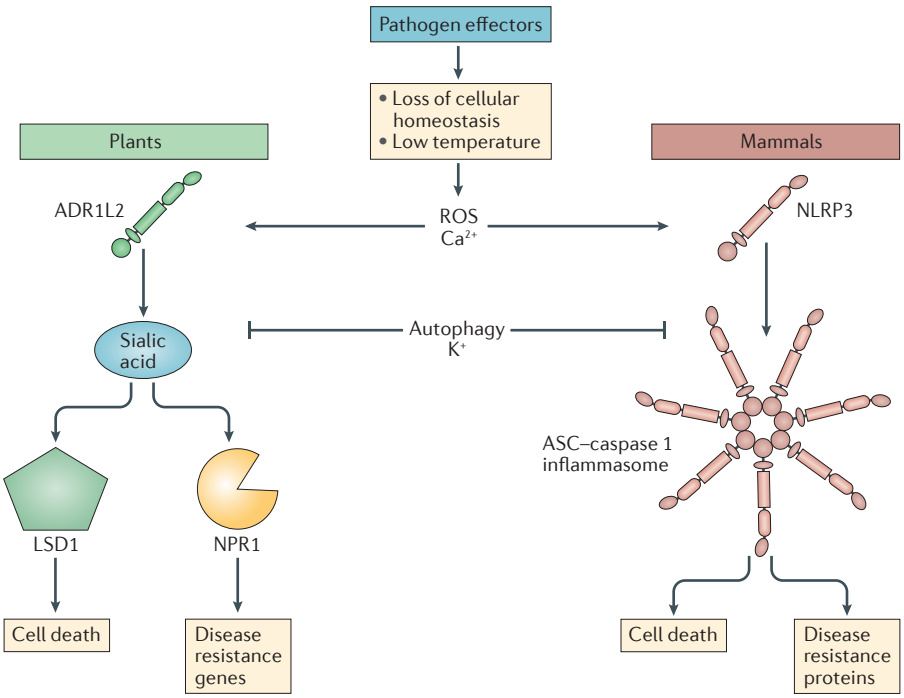

Figure 4 | **ROS production as a HAMP that triggers innate immunity in plants and mammals.** Pathogen effectors can trigger a loss of cellular homeostasis associated with reactive oxygen species (ROS) production in the cytoplasm of plant or mammalian cells. This functions as a signal that triggers the activation of nucleotide-binding site leucine-rich repeat (NBLRR) proteins (for example, the plant ADR1 family) or NOD-like receptors (NLRs; for example, mammalian NLRP3 (NOD-, LRR- and pyrin domain-containing 3)). This leads to cell death or to the induction of anti-pathogen defences, via separate mechanisms. Low temperature, calcium mobilization, potassium efflux and defective autophagy are all processes that have a similar effect on these evolutionarily separate systems of detecting ROS-based homeostasis-altering molecular processes (HAMPs). ADR1L2, ADR1-like 2; LSD1, lesion simulating disease 1; NPR1, non-expresser of pathogenesis-related genes 1.

specialized pathogens evade triggering the HAMP receptors, either by preventing the induction of HAMPs (for example, by avoiding the initiation of ER stress or altered phosphorylation of host components) or by specifically crippling downstream signalling pathways. A recent example of a pathogen counter-regulatory system is YopM, which is produced by *Yersinia* species and recruits the host kinases PKN1 and PKN2 to phosphorylate pyrin, thereby preventing the activation of the pyrin inflammasome[41].

Prediction 3. A third prediction is that the immune system will contain 'counter-counter-regulatory' systems. In the 'evolutionary arms race' between pathogens and hosts, ever more sophisticated detection and evasion networks evolve. In the adaptive immune system, the evolution of MHC class I for the presentation of viral antigens to $CD8^+$ T cells led to the evolution of a plethora of viral proteins that target MHC class I for degradation, allowing viruses to avoid detection by $CD8^+$ T cells[42]. However, there is a host defence to this counter-regulatory system, as NK cells detect the loss of MHC class I and drive antiviral responses. Similarly, we predict that counter-counter-regulatory networks will exist that detect the loss of HAMP receptors (FIG. 5). In this regard, it is notable that a homologue of pyrin, pyrin domain-containing protein 1 (PYDC1; also known as POP1), is a negative regulator of inflammasome activation[43]. It is possible that such negative-regulatory homologues function as a counter-counter-regulatory system in which, for example, pathogen-mediated cleavage of pyrin to prevent inflammasome activation would also cleave PYDC1, inadvertently triggering inflammasome activation (FIG. 5).

HAMPs and inflammatory disease

Does HAMP recognition contribute to inflammatory disease development? The evolution of a HAMP recognition cascade provides a potent tool in the immunological arsenal against pathogens, but it also elevates the risk of inflammatory diseases. Unlike classical pathogen recognition, which is based on recognizing PAMPs that are not produced by mammalian cells, there is the potential for HAMPs (or DAMPs) to be generated in the absence of a pathogen. Although viral infections can trigger ER stress and bacterial toxins can alter the phosphorylation balance of the cell, non-infectious cellular stresses can also affect these same pathways, potentially activating the inflammatory response. The risk that the HAMP pathway poses of triggering inflammation in a sterile manner suggests that this pathway may hypothetically contribute to the pathophysiology of inflammatory disease. The inflammatory diseases of ageing (neurodegeneration, metabolic and cardiovascular diseases) are major sources of mortality and morbidity, and each is characterized by the progression of sterile homeostatic defects to a pathological inflammatory state. There are multiple potential links between HAMPs and inflammatory disease, such as the role of ER stress in triggering NLRP3-mediated inflammation during steatohepatitis[44]. Below, we focus on Alzheimer disease as a potential paradigm for inadvertent triggering of the HAMP detection pathway. Although this connection is based on conceptual synergies, rather than empirical data, it shows the risks to the host of using HAMP detection as a pathogen recognition system.

HAMP recognition in the pathology of Alzheimer disease. There is growing recognition that Alzheimer disease includes a strong inflammasome component[45]. Genome-wide association studies are identifying unexpected linkages to inflammatory genes as well as expected linkages to sets of neurological genes[46]. Autopsy studies[47] and mouse models[48,49] both indicate an association of inflammation with clinical progression, and immunotherapy is being actively pursued[50]. However, as yet there is not a satisfying explanation for the early cellular events of Alzheimer disease — notably, amyloid-β aggregation and tau hyperphosphorylation — and the widespread inflammation that marks the degenerative stage of the disease.

It has recently been proposed that infection may lie upstream of both events, with amyloid-β production and aggregation acting as an antimicrobial defence[51]. Alternatively, early cellular changes may create a niche in which infections become more common, and chronic infection may drive the inflammatory state[52,53]. The HAMP model leads to a third distinct hypothesis, in which the early events that disturb cellular homeostasis directly trigger inflammasome activation because of the lack of specificity

in the initiating events. For example, hyperphosphorylation of tau could lead to competitive 14-3-3 deployment away from pyrin, mimicking the effect of bacterial toxins that induce the dephosphorylation of pyrin[20,21]. Furthermore, amyloid-β aggregates are taken up through autophagy and trigger inflammasome activation via NLRP3 (REF. 54). These aggregates may directly function as HAMPs, or they may precipitate out a negative regulator of NLRP3 in a mixed aggregate[55]; in either case, this would initiate an inflammatory reaction in a sterile setting. In addition, mitochondrial oxidative stress, which is a feature of Alzheimer disease, triggers NLRP3 activation[56]. Chemical induction of mitochondrial oxidative stress enhances inflammation and cognitive decline in APP/PS1 mice (an animal model of Alzheimer disease), and this can be reversed through detoxification of mitochondrial hydrogen peroxide[57]. Hyperphosphorylated tau and diffuse amyloid plaques that develop in individuals without Alzheimer disease as a result of exposure to air pollution are also associated with inflammation and an IL-1 expression signature[58].

Together, these studies support the hypothesis that early cellular changes that occur during Alzheimer disease may trigger inflammasome activation through the HAMP detection pathway and may contribute to disease pathology. However, this hypothesis still requires experimental validation. Dissection of the molecular events that underlie the pathophysiology of Alzheimer disease, and other inflammatory diseases, may therefore be the key to elucidating the molecular basis of HAMP detection.

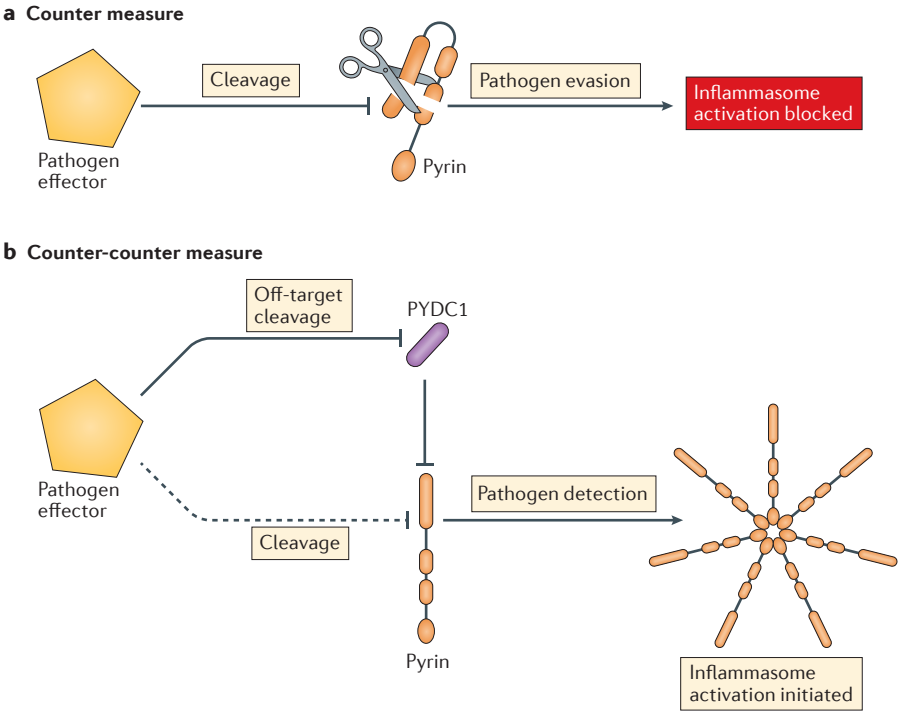

Figure 5 | **Theoretical models for counter-regulatory and counter-counter-regulatory systems in the detection of HAMPs. a** | The identification of homeostasis-altering molecular process (HAMP) detection systems in mammals suggests that specialist pathogens will have developed mechanisms to bypass detection, such as by cleavage of the signal integrator (for example, pyrin). **b** | In turn, host defences may have evolved mechanisms to detect such counter-regulatory systems. The existence of suppressive homologues of signal integrators (for example, pyrin domain-containing protein 1 (PYDC1; also known as POP1) may function as alternative routes to inflammasome activation; for example, if pathogen-mediated cleavage of pyrin also resulted in the cleavage of the suppressive homologue, this would still allow for inflammasome activation.

Conclusions

Effective immunity is essential for protection against pathogenic infections, but the consequences of unrestrained activation of immune mechanisms are pathological. This makes pathogen sensing an integral and crucial component of immunity. The innate immune system lacks the genetically encoded flexibility in pathogen sensing that characterizes the adaptive immune system, instead relying on a fairly small set of fixed receptors to determine the appropriate point for immune activation. Innate immune recognition is now appreciated to be increasingly sophisticated, relying on multiple independent processes to detect pathogens. PAMP detection was the first identified innate recognition process, in which a diverse set of receptors is used to detect the presence of molecular patterns that originate from infections. This concept was extended to DAMP recognition, which acts in a molecularly similar way, but with the molecular patterns originating from cellular death caused by pathogens rather than from the pathogens themselves. The detection of HAMPs further extends the repertoire of innate immune recognition mechanisms, with the identification of innate sensors, such as pyrin, that detect the functional consequences of pathogens on cellular processes, rather than simple molecular patterns generated by pathogens either directly or indirectly through tissue damage (TABLE 1). Although this sophistication markedly diversifies the set of pathogens that can be effectively identified, the complexity comes at a cost. PAMP receptors generally recognize molecules that cannot be produced by host cells; thus, aside from the chance of an inappropriate response to commensal microflora[59], the risk of inflammatory disease remains low. By contrast, DAMPs are produced by tissue damage regardless of the cause and, thus, they have the potential to drive pathological inflammatory responses, even in the setting of sterile injury[60]. HAMP detection further escalates the risk of inappropriate inflammation, with even a benign alteration of cellular homeostasis being theoretically capable of degenerating into a pathological inflammatory state. It is distinctly possible that deficiencies of the HAMP recognition system underlie many inflammatory diseases. The relationship between risk, potency and regulation in the PAMP–DAMP–HAMP axis is likely to explain the evolutionary cost–benefit of this sophisticated system.

Adrian Liston is at the Department of Microbiology and Immunology, University of Leuven, Leuven 3000, Belgium; and at the VIB Center for Brain and Disease Research, Leuven 3000, Belgium.

Seth L. Masters is at the Inflammation Division, The Walter and Eliza Hall Institute of Medical Research, Parkville, Victoria, 3052, Australia; and at the Department of Medical Biology, University of Melbourne, Parkville, Victoria 3010, Australia.

Correspondence to A.L
adrian.liston@vib-kuleuven.be

doi:10.1038/nri.2016.151
Published online 6 Feb 2017

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Competing interests statement
The authors declare no competing interests.