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REVIEW

Adaptation in the innate immune system and heterologous innate immunity

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Abstract The innate immune system recognizes deviation from homeostasis caused by infectious or non-infectious assaults. The threshold for its activation seems to be established by a calibration process that includes sensing of microbial molecular patterns from commensal bacteria and of endogenous signals. It is becoming increasingly clear that adaptive features, a hallmark of the adaptive immune system, can also be identified in the innate immune system. Such adaptations can result in the manifestation of a primed state of immune and tissue cells with a decreased activation threshold. This keeps the system poised to react quickly. Moreover, the fact that the innate immune system recognizes a wide variety of danger signals via pattern recognition receptors that often activate the same signaling pathways allows for heterologous innate immune stimulation. This implies that, for example, the innate immune response to an infection can be modified by co-infections or other innate stimuli. This "design feature" of the innate immune system has many implications for our understanding of individual susceptibility to diseases or responsiveness to therapies and vaccinations. In this article, adaptive features of the innate immune system as well as heterologous innate immunity and their implications are discussed.

Keywords Heterologous immunity · Innate immunity · Adjuvant · T cell · Inflammation · Contact dermatitis

Abbreviations

ACD	Allergic contact dermatitis
BCR	B cell receptor
CHS	Contact hypersensitivity
CLR	C-type lectin receptor
CRISPR	Clustered regularly interspaced short palindromic repeats
DAMP	Damage-associated molecular pattern
DC	Dendritic cell
DNP	2,4-Dinitrophenyl
DTH	Delayed type hypersensitivity
DNTB	2,4-Dinitrothiocyanobenzene
ECM	Extracellular matrix
MAMP	Microbe-associated molecular pattern
MDSC	Myeloid-derived suppressor cell
NK	Natural killer
NLR	NOD-like receptor
PAMP	Pathogen-associated molecular pattern
pMHC	Peptide/MHC complex
PRR	Pattern recognition receptor
RLR	RIG-I like receptor
SAR	Systemic acquired resistance
TCR	T cell receptor
TLR	Toll-like receptor
Treg	Regulatory T cell
TNCB	2,4,6-Trinitrochlorobenzene
TNP	2,4,6-Trinitrophenyl

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Introduction

The innate immune system responds immediately to infections, mechanical or chemical assaults which disturb tissue homeostasis. It recognizes a large variety of

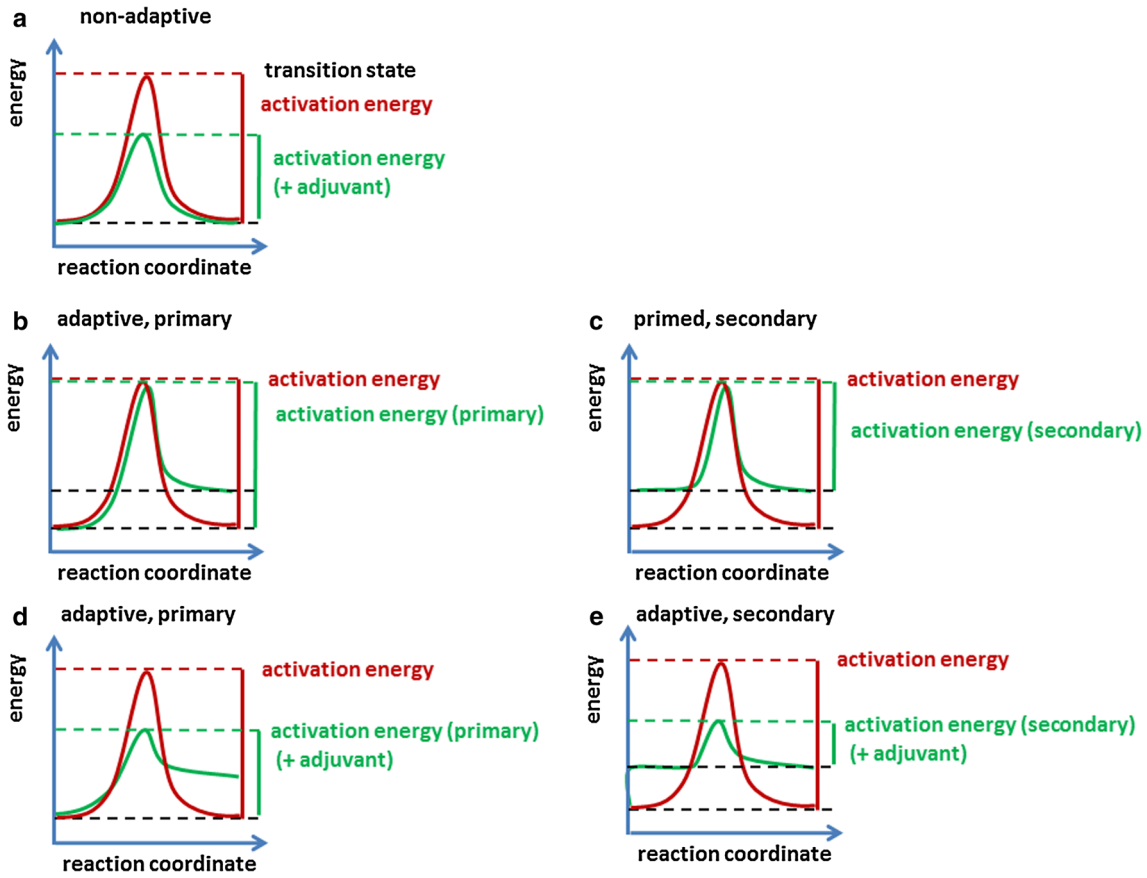

Fig. 1 Impact of heterologous innate immune stimulation on activation thresholds. An immune reaction can be compared with a chemical reaction. The activation threshold is determined by the activation energy, i.e., the energy difference between the basal energy level and the energy of the transition state. **a** In the case of a non-adaptive response, the immune system becomes activated and returns to the former, homeostatic energy level that has been established in a calibration process (*red line*). Heterologous stimuli (e.g., adjuvants) may act like catalysts and lower the energy level of the transition state thereby lowering the activation threshold of the primary response (*green line*). **b** If the system is primed by an immune response, it returns to a higher basal energy level in a primary response. **c** This lowers the activation energy required for the secondary response (*green line*). **d** Heterologous stimulation (e.g., by adjuvants) can lower the activation threshold of the primary response and the system can be primed in addition (*green line*). **e** The result is an even lower activation energy required for the secondary response (*green line*)

microbe- (MAMPs) or pathogen-associated molecular patterns (PAMPs) as well as exogenous and endogenous non-microbial danger signals such as damage-associated molecular patterns (DAMPs). These danger signals trigger germline-encoded pattern recognition receptors (PRRs) such as the Toll-like receptors (TLRs) [1–5]. PRR triggering leads to an innate inflammatory response that aims at the restoration of homeostasis and repair of tissue damage. Moreover, this response is a prerequisite for efficient activation of the adaptive immune system, e.g., the priming of naïve T cells by activated dendritic cells (DCs) [6].

Adaptive features as illustrated by affinity maturation, receptor editing and formation of memory cells were always attributed exclusively to the T- and B lymphocytes of the adaptive immune system [7–11]. However, in recent years evidence for adaptive features of the innate immune system is accumulating. These manifest themselves, for example, in a heightened reactivity of innate immune cells following a primary immune response (Fig. 1). Another interesting feature of the innate immune system is the fact that different members of a given PRR family feed into the same or similar signaling pathways. This enables heterologous innate immune stimulation [12] leading, for example, to the amplification of innate signaling by a pathogen through additive or synergistic activation of the same pathways via different PRRs due to co-infection with different pathogens (Figs. 2, 3).

Adaptive immune features are also found in bacteria and invertebrates. Bacteria use the clustered regularly interspaced short palindromic repeats (CRISPR)-Cas system to induce adaptive immunity [13]. They incorporate sequences from foreign genetic elements such as viruses and plasmids as spacers (CRISPR spacers) into

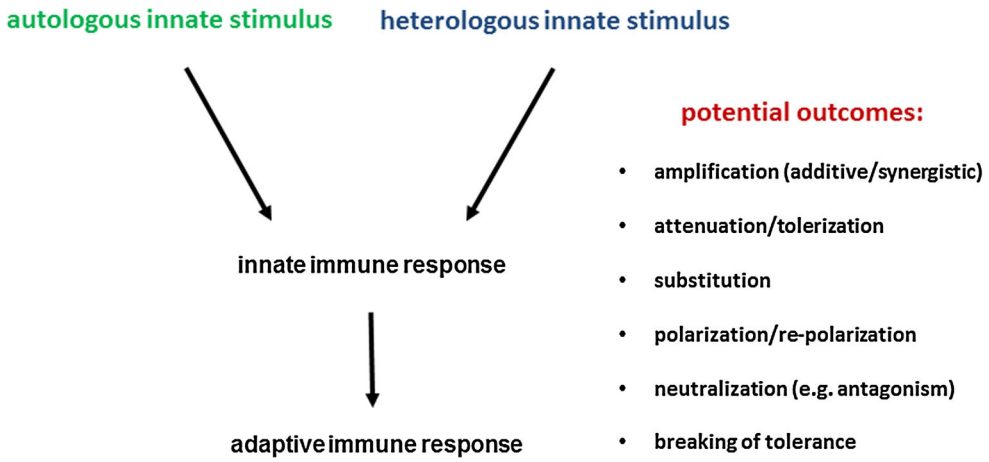

Fig. 2 Principle of autologous and heterologous innate immune stimulation and potential outcomes of heterologous innate immune stimulation. As an example, upon infection autologous stimuli are associated with the pathogen trigger PRRs such as TLRs (e.g., LPS via TLR4). Co-infection or tissue damage can provide heterologous stimuli acting via the same or different TLRs (e.g., DNA via TLR9). This can lead to different potential outcomes

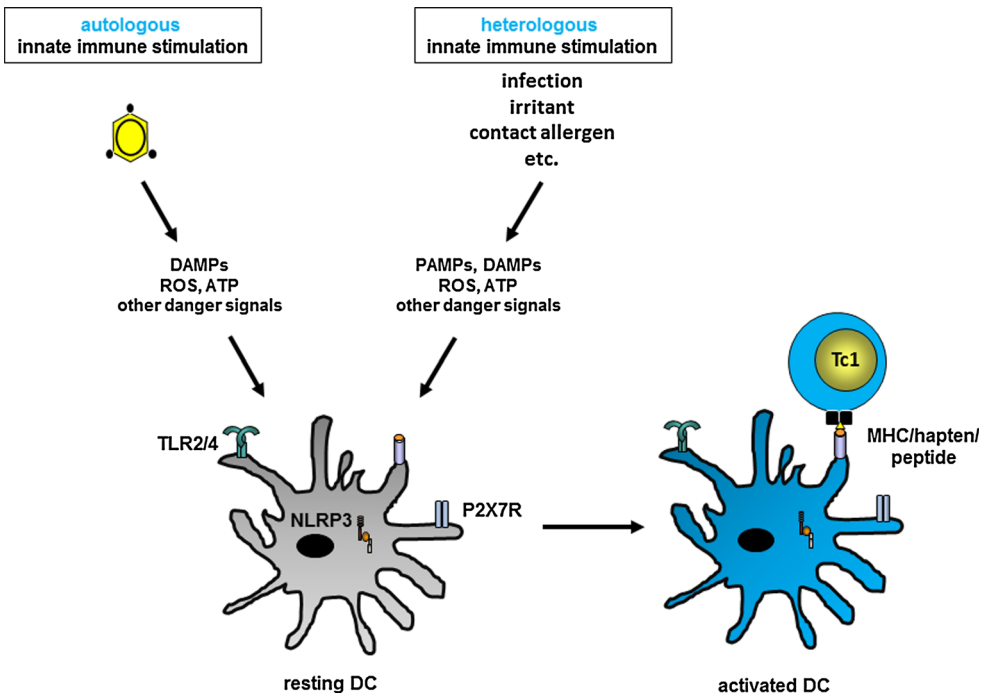

Fig. 3 Heterologous innate immune stimulation in allergic contact dermatitis. Contact allergens either directly or indirectly trigger PRRs to cause production/release of other danger signals including ROS and ATP. Combinations of contact allergens, addition of irritants or co-infections can provide heterologous innate immune stimulation leading, for example, to additive or synergistic amplification of the innate inflammatory response

an array of endogenous repeat sequences (CRISPR repeats). CRISPR loci are flanked by CRISPR-associated (Cas) genes. Transcription of these loci results in the production of small interfering RNAs. These bind to complementary sequences, which are then targeted and degraded by Cas endonucleases. Moreover, invertebrates use RNA interference to generate immunity to infection [14, 15].

Innate adaptation resulting in "trained" innate immunity [16] and heterologous innate immunity are important in our understanding of individual disease susceptibility, responsiveness to therapies or vaccinations. Most importantly, these features open up many possibilities to modulate innate and, subsequently, adaptive immune responses in the treatment of disease and in vaccination strategies. This may be achieved, for example, by altering activation thresholds and using positive or negative stimulatory adjuvants as heterologous innate immune stimuli to promote immunity or tolerance.

This article gives a point-of-view on the "design" and function of the innate immune system with a focus on adaptive features and heterologous innate immunity.

Calibration of the adaptive immune system

The adaptive immune system consists of T- and B cells with highly diverse clonotypic antigen-specific T cell (TCR) and B cell receptors (BCR), respectively. Activation thresholds for T cells are being defined during thymic selection. T cells, which receive survival signals by low-affinity interactions of their TCRs with self-peptide/MHC complexes (pMHC) are positively selected [17]. In the periphery tonic signaling triggered by self-pMHC ensures T cell survival and increased antigen reactivity [18, 19] as well as maintenance of functional memory T cells [20]. The BCR is capable of ligand-independent tonic signaling that regulates B cell survival and differentiation [21, 22]. One of the hallmarks of adaptive immunity is the generation of long-lasting antigen-specific memory. This enables a fast recall response to repeated challenges with previously encountered antigens by recirculating and tissue-resident high-affinity T- and B cells [9, 23–25]. Due to the selection of high-affinity receptors and the independence of co-stimulatory signals, the threshold for the activation of memory T cells is significantly lower.

Calibration of the innate immune system

As in the adaptive immune system, activation thresholds are established for innate immune responses (Fig. 1). This is achieved by a calibration process that involves continuous exposure to homeostatic microbial signals from commensal bacteria at barriers such as skin, lung or gut [26, 27]. In addition, continuous exposure to endogenous danger signals generated during normal cell and extracellular matrix (ECM) turnover might contribute to this calibration process [28–30]. A further calibration system is based on the sensing of endogenous viruses integrated as retroelements into the genome [31]. Cyotosolic DNA sensors can be activated by cDNA intermediates of such retroelements. The sensitivity of this system has to be adjusted such that autoreactivity is prevented without compromising immune responses to DNA viruses and retroviruses such as HIV. Relevant cytosolic DNA sensors are IFI6 or the cyclic GMP-AMP synthase cGAS [32]. These eventually trigger the production of type I interferon production via the ER transmembrane protein STING. Autoreactivity of the innate immune response to endogenous retroelements is prevented in part by enzymes that metabolize cDNA intermediates. Mutations in such enzymes, however, leads to their accumulation and can cause disease. One example is the mutation of the exonuclease Trex1 as found in Aicardi–Goutières syndrome or some forms of systemic lupus erythematosus (SLE) [31]. In this case, accumulation of endogenous DNA triggers the cGAS-STING axis and activation of interferon-stimulated genes. This was prevented in cGAS knockout mice [33]. Moreover, derepression of endogenous retroelements by UV light may cause inflammation.

Thus, the innate immune system must maintain a delicate balance that prevents "self-reactivity" to commensals, endogenous danger signals such as DAMPs or endogenous retroelements under homeostatic conditions and at the same time allows to react to infection or tissue damage. Similar to tonic TCR signaling which preserves antigen reactivity in the naïve T cell pool, tonic innate immune receptor signaling may keep the innate immune system in a more reactive, alert state.

Commensal bacteria are very important in the calibration of the innate immune system. Apart from defects in the development and maturation of the immune system in germ-free mice, the overall fitness of the innate immune system is compromised in their absence [27]. Antibiotic-treated mice have disrupted commensal bacterial communities. Innate immunity at barrier surfaces is impaired as shown, for example, by reduced innate antiviral responses to influenza infection. The production of pro-inflammatory cytokines and chemokines including inflammasome-dependent IL-1β production as well as the type I interferon (IFN) response is compromised [26, 34]. At the cellular level, it has been shown that innate-like lymphocytes such as marginal zone B cells recognize circulating bacterial products with adjuvant properties. They express polyreactive BCRs as well as TLRs that recognize diverse microbial patterns. They are in a pre-activated, primed state and rapidly respond to blood-borne antigens. This primed state seems to depend on circulating microbial products, since germ-free mice have impaired natural antibody responses [35]. Similar priming by commensal-derived signals has been shown for mononuclear phagocytes [36]. Germ-free mice have strongly impaired expression of inflammatory response genes including type I IFNs in these cells from non-lymphoid organs. This is due to the lack of activating histone marks in the cytokine gene promoters preventing binding of the translocated transcription factors NF-κB and IRF3. As a consequence, NK cells are not appropriately primed and antiviral immune responses are compromised. These findings indicate that systemic effects on innate immune fitness are mediated via circulating bacterial products with adjuvant properties.

In summary, the innate immune system is calibrated by commensal microbiota and, most likely, endogenous signals to ensure tissue homeostasis, tissue repair and responsiveness to infections and other, non-infectious challenges. Such challenges can cause priming of innate immune cells, which lowers their activation threshold and keeps the innate immune system poised for more rapid and more efficient responses (Fig. 1).

Other means to lower activation thresholds are the depletion or functional impairment of immunoregulatory cell populations such as regulatory T cells (Treg), invariant NKT cells (iNKT) or myeloid-derived suppressor cells (MDSC) [37–40]. Moreover, genetic defects in pathways that prevent inflammation decrease activation thresholds. An example is Nrf2-deficient mice with a deficient antioxidant phase 2 response. Due to their heightened pro-inflammatory state, chemical-induced skin irritation or allergic contact dermatitis (ACD) are more easily triggered [41].

Mechanisms of adaptation in the innate immune system

Adaptation of the innate immune system to assaults can be due to transient or stable changes in chromatin conformation and microRNA (miRNA) profiles leading to altered gene expression patterns. Thereby, previous immunologic experience can be memorized over a longer period of time. Plants lack an adaptive immune system, but they also recognize PAMPs/MAMPs using PPRs including TLR- and NLR-like receptors [42, 43]. Recognition of PAMPs/MAMPs and other forms of biotic and abiotic stress results in defense priming in plants. This is characterized by a heightened state of resistance and faster and stronger responses to stress including infection. The local response can be transmitted systemically due to systemic acquired resistance (SAR) mediated by plant hormones such as salicylic acid [44]. This innate plant defense system thus exerts adaptive features. The underlying mechanisms include epigenetic modifications that can be heritable [45–47].

Interestingly, short-term innate memory has also been described for immune cells [48]. Histone modifications, some forms of transient DNA methylation and changes in the expression of miRNAs have been identified as potential mechanisms. Epigenetic modifications in macrophages induced by TLR signaling have been reported in the mouse system of LPS tolerance [49]. Here, both silencing of pro-inflammatory and priming of antimicrobial genes was detected identifying an innate immune response with features of adaptive immunity. Such mechanisms may also contribute to the adaptive features of other innate immune cells like NK cells [50]. For NK cells' memory, T cell-like functions have been identified in antiviral immunity and chemical-induced ACD [51–57]. Monocytes may also display memory-like features [58]. It was shown that T/B cell-deficient mice were protected against reinfection with *Candida albicans*. This was dependent on monocytes, which exhibited increased cytokine production. Epigenetic changes were suggested to be responsible for this "trained" innate immune response [16, 59]. Interestingly, similar epigenetic modifications in monocytes were observed following *Bacillus Calmette Guérin* (BCG) vaccination against tuberculosis [60]. This may explain in part the non-specific protective effects of the BCG vaccine on unrelated infections [61, 62] and provides an example for heterologous innate immunity.

Memories of the past: does the tissue memorize previous immune responses?

It is conceivable that the different tissues and organs of an organism can adapt to different immune stimuli. Barrier tissues such as skin, lung or gut adapt to the commensal microbiota. This adaptation process is essential for the establishment of immune homeostasis [27, 63–65]. Disturbance of the microbiota can result in the induction of disease as a consequence of dysbiosis [66–68]. Restoration of a healthy microbiota achieved, for example, by fecal microbiota transplantation (FMT) can ameliorate disease states [69]. In addition, acute and chronic infections may leave traces in the tissue in the form of transient or long-term adaptation processes that may be imprinted by epigenetic modifications such as histone and DNA modifications and altered miRNA expression profiles. Infections may thus shape immune responses to heterologous infections and other challenges at different levels. Eventually, the tissue may be more responsive, poised to react more quickly due to a heightened inflammatory state and, thereby, lowered activation thresholds. Consequently, the quality of the immune response to new, heterologous challenges may be altered. In the case of chronic infections, subsequent immune responses are often impaired [70]. This may indicate an adaptation process that serves to prevent immunopathology by downregulation of immunity. Moreover, the type of immune response may be altered due to changes in the cytokine milieu. As a consequence, the polarization of DC cytokine and co-stimulatory/co-inhibitory receptor expression profiles can be altered affecting the polarization of T cell responses induced by these DCs in local draining lymph nodes, and the reactivity of tissue-resident memory T cells [11] and of other resident or infiltrating immune cells. Moreover, alterations in chemokine profiles may impact the type of immune cells that can be recruited into the tissue. In addition, the existence of tissue-resident memory T cells may be explained in part by sustained chemokine production by tissue cells as part of innate memory-like features [71–73]. The sustained production of CCL27 by keratinocytes is one example. Thus, retention of CCR10 expressing skin homing T cells may underlie the phenomenon of recall contact dermatitis or flare-up reactions at the site of the first contact allergen antigen encounter upon re-challenge with the same contact allergen at a different site [74–76].

Adaptation and susceptibility to allergies

Infections influence the susceptibility to allergy and atopy. This was formulated in the hygiene hypothesis [77]. Today, it is clear that besides genetic predisposition that correlates in part with polymorphisms in innate immune receptor genes such as TLR- and NLR genes [78, 79], exposure to infectious agents and other environmental factors is a critical determinant for susceptibility. Epidemiological evidence shows a correlation of increased hygiene, i.e., reduced microbial exposure, and the rise of allergic and autoimmune diseases [80], but many controversial issues remain to be investigated further [81, 82]. Exposure to infections shapes the innate immune system and subsequently polarizes the T cell response [83]. Pre-natal microbial farm exposure as well as early life exposure and consumption of unprocessed cow's milk reduces the risk of asthma development [84]. These exposures correlated with an upregulation of TLRs and a bias of the T cell response towards a Th1 rather than a Th2 type [85, 86]. This adaptation and polarization of the pre-natal and perinatal immune system was reflected in epigenetic modifications in asthma candidate genes [87]. Studies in mice have revealed that specific bacteria such as *Acinetobacter lwofii* or *Staphylococcus sciuri* W620 as contained in stable dusts in part explain the effects and drive epigenetic modifications, for example, in Th1/Th2-relevant cytokine genes [88–91]. In these studies, a protection of the offspring from airway hyperreactivity was observed when pregnant female mice were exposed to such bacteria. The effect was dependent on maternal expression of Toll-like receptors (TLR) [91, 92]. In addition, intestinal microbiota contributes to the protective effects [93]. Thus, antibiotic-treated mice or germ-free mice revealed higher IgE levels and higher levels of circulating basophils suggesting a role for the commensal microbiota [94]. Interestingly, mice with a B cell-specific defect of MyD88 had a similar phenotype arguing for a contribution of TLR signaling in B cells in shaping the immune system and determining susceptibility to allergies. These findings from mouse and human studies contribute to our understanding of gene–environment interactions and the influence of hygiene in influencing the susceptibility for atopic diseases and asthma [95, 96] by impacting the adaptation and polarization of the innate and, consequently, adaptive immune response.

In general, immune responses are shaped individually owing to the fact that our immune system is not naïve and is modulated transiently or stably by previous or current experience due to adaptation [97]. The innate immune system does not only adapt to its exposures by calibration and heightened reactivity, but also by polarization that translates into the type of T cell response due to T cell subset differentiation. Therefore, individually different immune history and experience and the resulting conditioned tissue or systemic immune microenvironments may in part explain the differences in disease susceptibility and responsiveness to therapies as well as overall immune reactivity. It remains to be determined whether these parameters are also influenced by the great inter-individual variability regarding commensal communities that impact basal calibration and maybe also polarization of the immune system [27, 98].

In summary, the adaptation of the tissue microenvironment to immune challenges, including pre-natal and perinatal innate immune stimulation, by microbial exposure can significantly shape immune responses to future challenges.

Heterologous innate immunity

The innate immune system is typically activated via PRRs. The most prominent PRR families are the TLRs, NOD-like receptors (NLRs), C-type-lectin receptors (CLRs) and RIG-I-like receptors (RLRs) [5, 99–102] and a variety of DNA sensors [32, 103, 104]. These PRRs recognize a diverse array of microbial and non-microbial lipids, proteins, nucleic acids or carbohydrates as danger signals. This broad specificity of PRRs allows the innate immune system to mount similar responses to a diverse array of pathogens, thereby ensuring appropriate immune defense as well as the restoration of tissue homeostasis.

The disadvantage of the restriction of clonotypic TCR- and BCR expression to single cell lineages and of their exquisite antigen specificity is the low cell number specific for a given antigen in primary immune responses. As a consequence, after an infection the necessity for priming, differentiation and expansion of the few naïve T- or B cells with distinct antigen specificity delays an efficient adaptive immune response by days. This time gap is bridged by the immediately activated innate immune system. The advantage of the innate PRR system is that the same PRRs can be found on many different cell types such as innate immune cells and also on non-hematopoietic tissue cells such as epithelial and endothelial cells as well as on T- [105] and B lymphocytes [106]. Different cell types can thus be simultaneously activated by the same array of PAMPs, MAMPs or DAMPs allowing for the generation of a strong and immediate innate immune response. Due to the triggering of the same or similar signaling pathways by different PRRs such as the 10 human and 13 murine functional TLRs, additive or synergistic triggering of several TLRs by ligands that may derive from different sources allows for amplification of innate immune responses (Fig. 4). This make-up of the innate immune system provides the basis for heterologous innate immunity.

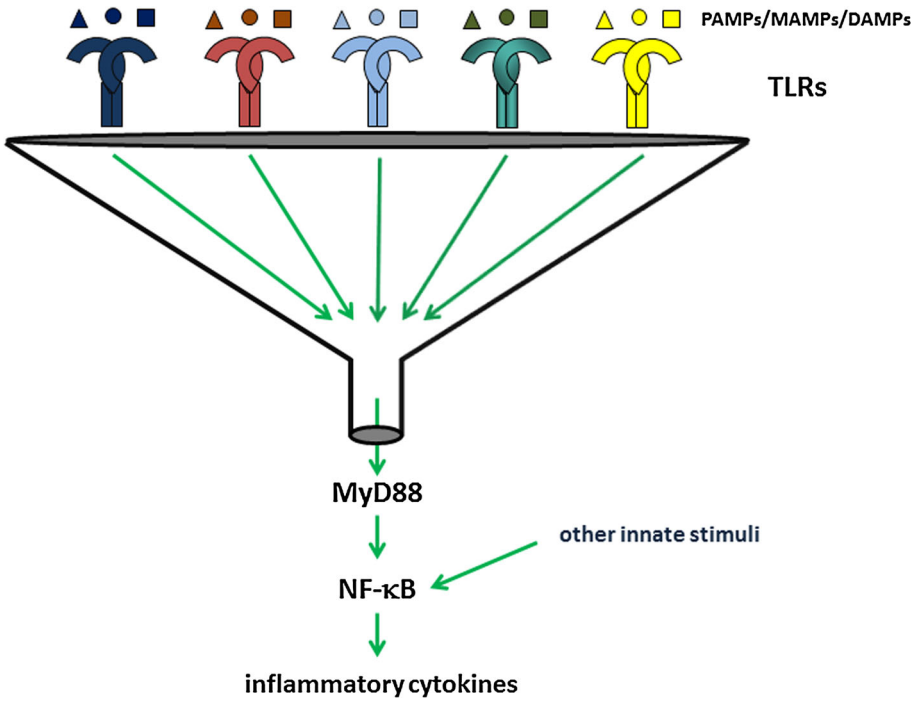

Fig. 4 Funnel function of TLRs for innate signaling and heterologous innate immunity. Almost all TLRs signal by assembling a signaling complex containing the adaptor protein MyD88. As a result activation of NF-κB and induction of its target genes including the inflammatory cytokines IL-6, IL-12 and TNF-α occurs. MAP kinases and interferon regulatory factors (IRFs) can also be induced. Other, TLR-independent innate stimuli may also trigger the NF-κB pathway

Heterologous immunity was originally defined as cross-reactivity of memory T cells specific for one infectious agent to a new infectious agent or to alloantigens thereby impacting the outcome of heterologous infections, transplantation tolerance and autoimmunity [107–109]. It was shown that cross-reactive T cells can determine the individually different outcomes of a heterologous infection. As an example, mice infected with influenza virus and then later on with lymphocytic choriomeningitis virus (LCMV) developed pneumonitis of various degrees. The severity of the disease directly correlated with the frequency of T cells cross-reactively recognizing epitopes from influenza and LCMV [110].

Heterologous innate immune stimulation can be defined as the triggering of similar or identical signaling pathways, for example, via the same or different PRRs, by danger signals not derived from the original pathogen or agent that induces innate and often adaptive immunity (Figs. 2, 3). In the case of co-infections, heterologous innate stimuli can occur in addition to or instead of the autologous stimuli. Potential outcomes can be additive or synergistic amplification or attenuation/tolerization, substitution, neutralization (e.g., by antagonism), re-polarization of immune responses or breaking of tolerance (Figs. 2, 3) [111, 112]. Another outcome due to a longer-lasting adaptation of the innate immune system to vaccination can be an improved ability of the immune system to handle heterologous infections [61]. These features of the innate immune system can be beneficial or detrimental.

Heterologous innate immunity may explain the impact of previous or current acute or of chronic co-infections on the outcome of innate and adaptive immune responses to a distinct infection [70, 113] or other assaults. Examples are the cross talk of *Streptococcus pneumoniae, Staphylococcus aureus* and influenza virus in lung infections [114, 115]. A recent study demonstrated synergistic lethal effects of an established influenza infection of mice upon co-infection with *Legionella pneumophila* [116]. In this study, co-infection caused severe damage to the lung tissue. This was associated with the downregulation of genes involved in tissue protection and repair specifically in the co-infected animals. Interestingly, in mice lacking TNF, caspase-1, TLR2/4, MyD88 or nitric oxide synthase (Nos)2 or after depletion of Gr-1+ or NK1.1+ cells the lethality was not significantly altered. These data demonstrate a synergistic heterologous effect involving infection-induced tissue stress and damage responses. Lethality was due to an irreversible loss of tolerance to tissue damage upon co-infection. Most interestingly, these effects were independent of pathogen burden and the level of innate inflammation, at least for the parameters measured.

Specificity of the innate immune response and heterologous innate immunity

The exquisite antigen specificity of clonotypic TCRs on T cells is illustrated by the ability of human T cells to differentiate between the contact allergens 2,4-dinitro- (DNCB) and 2,4,6-trinitrochlorbenzol (TNCB) [117]. Penicillin-specific human T cells are able to recognize

small differences in the side chains of derivatives of this β-lactam antibiotic [118]. Clonotypic TCRs also recognize differences in the amino acid sequence of short antigenic peptides and amino acid modifications.

Despite the notion that a broad spectrum of molecular patterns is recognized by PRRs, they also exhibit ligand specificity. The variety of PRRs recognizes a multitude of different ligands. Individual PRRs, however, exert specificity up to the level of recognizing small molecular differences in ligands, which impact signaling and the resulting response as revealed by the recognition of lipid A variants by the TLR4–MD2 complex [119–121] or the differentiation between fucose and mannose by DC-SIGN [122]. Nevertheless, many different PAMPs and DAMPs are assigned as activators to the same TLR. Different ligand-binding mechanisms have been identified for different TLRs [123]. This may also hold for individual TLRs and explain the diversity of activating ligands for a single TLR.

One very important notion is that similar activation and polarization of DCs with respect to their T cell subset polarizing properties can be achieved by the autologous or heterologous stimulation of different PRRs. This is the key to heterologous innate immune stimulation and allows the innate immune system to flexibly mount similar immune responses to various challenges. In addition, the simultaneous interplay of different TLRs enables fine tuning of the response [124, 125].

The "immunologists dirty little secret" [1] describes the use of heterologous innate immune stimulation in the form of adjuvants for vaccination. The efficient induction of memory responses is the goal of vaccination strategies. In this context, the innate immune system is of great importance for the design of efficient vaccines [126] due to its crucial impact on the activation and polarization of adaptive immune responses [6, 127]. Few adjuvants are licensed for clinical use [128]. They include monophosphoryl lipid A (MPLA) or alum and target TLRs and the NLRP3 inflammasome. Other adjuvants that target RLRs and other nucleic acid sensors are in development [126, 129]. Interestingly, the PAMPs used in vaccines and even more so in experimental studies are often not derived from the target pathogens of the vaccination. This demonstrates the practical relevance of heterologous innate immune stimulation [130, 131]. Attenuated vaccines, however, use the pathogens' own PAMPs for innate immune receptor signaling addressing various innate immune receptor families [126]. In addition, live vaccines contain so-called vita-PAMPs such as bacterial mRNA, which makes them more efficient than dead vaccines [132]. It will be interesting to study the impact of the composition of heterologous innate immune stimuli on the outcome of vaccinations. Including vita-PAMPs as adjuvants may increase their efficiency.

In addition to triggering T- and B cell responses directed against the target pathogen, unspecific immune stimulation has been shown for vaccines such as the tuberculosis vaccine BCG, measles vaccine and vaccinia virus vaccine [61]. These positive effects are due to adaptation as a consequence of heterologous immunity including both cross-reactive T cells and so-called *trained innate immunity* [133].

In summary, the rather broad specificity of the innate immune response regarding the diversity of stimuli that can trigger similar outcomes explains why heterologous innate immune stimulation is an important issue to be considered in our understanding of diseases, of therapeutic immune interventions and of vaccination strategies.

Role of PRRs in heterologous innate immunity

The broad specificity of the innate immune system is well illustrated by the diverse array of microbial or endogenous ligands triggering the different mouse and human TLRs. These include proteins, lipids, nucleic acids and carbohydrates. The immune response resulting from the triggering of different TLRs is very similar due to the fact that all TLRs except for TLR3 signal via the adaptor protein MyD88 to activate NF-κB and MAP kinase signaling. TLR4 and TLR3 also signal via the adaptor Trif to induce type I IFNs [5, 28]. Likewise, the great variety of activators for the NLRP3 inflammasome triggers caspase-1 activation and processing of immature pro-IL-1β and pro-IL-18 to their bioactive and secreted forms [134, 135]. RIG-I and MDA5, cytosolic RLRs recognizing RNA from many different sources, signal via the adaptor MAVS to activate NF-κB and IRF3 signaling pathways [136] and the NLRs NOD1 and NOD2 engage the adaptor proteins RIP2 and CARD9 to signal via NF-κB and MAPK and AP1, respectively [137, 138]. Thus, the huge variety of PAMPs and DAMPs elicits similar innate immune responses due to a funnel function of the PRR families that focus the perception of exogenous and endogenous danger signals on a limited number of signaling pathways driving the innate inflammatory response (Fig. 4). For this reason, different combinations of PAMPs and PRRs can result in similar innate inflammatory responses. With respect to the activation and polarization of T cell responses by DCs, this also implies that different TLRs on a given DC can be triggered to yield the same polarized T cell response. The make-up of the innate immune system, therefore, allows for a complete uncoupling of innate and adaptive specificities. This means that the DC that primes and polarizes an antiviral or antibacterial T cell response does not necessarily have to be activated by danger signals represented by PAMPs derived from the pathogen that the T cell

response is directed to. Heterologous innate immune stimulation may substitute for the autologous PAMPs (Fig. 4). This notion has a number of implications including additive or synergistic effects of the simultaneous triggering of several TLRs [124]. This may allow overcoming activation thresholds not reached by weak stimulation of a single TLR. In addition, TLR-independent heterologous stimuli can play an important role by triggering the same or other pro-inflammatory innate signaling pathways (Fig. 4).

Heterologous innate immune stimulation and contact dermatitis

Heterologous innate immune stimulation has many implications regarding its potential outcomes (Figs. 2, 3) including the substitution of missing autologous innate stimuli or the amplification of autologous stimuli as exemplified for ACD [111, 112, 139], a sterile inflammatory response induced by protein-reactive metal ions and organic chemicals, but they should be of general importance for immune reactions. ACD is a hypersensitivity reaction of the skin to chemicals. The main effector cells are T cells of the CD4+ Th1/Th17 and CD8+ Tc1/Tc17 subsets. Contact allergens differ in their allergenic potency as determined, for example, in the local lymph node assay (LLNA) by their ability to induce cell proliferation in skin draining lymph nodes following repeated epicutaneous application [140]. The potency seems to correlate with chemical reactivity and the strength of the innate inflammatory response that is induced and translated into the vigor of the T cell response and the allergic reaction [141]. Contact allergens activate the innate immune system directly or indirectly. Direct activation of human TLR4 was shown for nickel and cobalt. These metal ions bind to histidine residues that are present in human but not mouse TLR4 leading to TLR4 dimerization that is essential for signaling, which occurs in the absence of LPS [142, 143]. Palladium also seems to activate human TLR4 [144]. As shown in the contact hypersensitivity (CHS) mouse model, indirect PRR activation by organic chemicals such as TNCB and oxazolone depends on the generation of endogenous danger signals. This was shown for the triggering of TLR2 and TLR4 by fragments of the ECM component HA [145, 146] and for the NLRP3 inflammasome via extracellular ATP and signaling via the purinergic receptor P2X7R [147–149]. ROS are also induced by contact allergens and are required for CHS [146]. Similar pathways are triggered by acetaminophen in drug-induced liver injury (DILI) [111, 150].

Activation thresholds for the innate immune system are often not reached by potential contact allergens and sensitization, i.e., the priming of contact allergen-specific T cells does not occur. In order to exceed the threshold and to induce sensitization to such allergens repeated or chronic exposure may result in cumulative inflammatory stimuli. In addition, heterologous innate immunity is of great importance (Fig. 1) [12, 113]. Thus, additive or synergistic effects by the combination of different contact allergens or allergens and irritants may result in (facilitated) sensitization. Examples are the amplification of proliferative responses to sub-sensitizing concentrations of the strong contact allergen DNCB by sodium dodecyl sulfate (SDS) [151], amplification of sub-threshold inflammation of suboptimal, non-sensitizing doses of TNCB by oxazolone [152] or the observed amplification effects in human ACD due to combinations of weak contact allergens such as fragrances or of contact allergens and irritants [153–155]. Toxicological hazard identification and risk assessment are mostly performed with single substances. However, heterologous innate immune stimulation must be considered whenever substances are combined. Consumer products such as cosmetics are usually complex mixtures and formulations. Similar aspects apply to some drugs. In addition, consumers and patients often simultaneously use several products and drugs, respectively. Due to the fact that the contact allergen that induces sensitization does not necessarily have to provide the autologous innate stimuli that appropriately activate and polarize the antigen-presenting DCs, heterologous stimuli can amplify insufficient or substitute for absent contact allergen-dependent innate immune stimulation. Thus, even non-allergens such as irritants or infections may provide such stimuli (Fig. 3). Examples are the conversion of nickel, a non-allergen in mice, to an allergen by providing exogenous danger signals such as PAMPs like LPS (Fig. 5a) or the irritant SDS [156, 157] or the conversion of the weak contact allergen/tolerogen 2,4-dinitrothiocyanobenzene (DNTB) into an allergen by addition of SDS [158]. Interestingly, the combination of the antibiotic amoxicillin with TLR ligands results in a significant increase in DC maturation, IL-12 production and T cell proliferation in vitro, mainly with cells from patients with DTH responses to the drug [159]. This suggests that drug-induced maculopapular exanthema reactions may be exacerbated by heterologous innate stimuli.

The findings in the CHS model demonstrate that heterologous innate stimuli can substitute for missing autologous innate stimuli, thereby leading to innate immune responses or the breaking of immune tolerance, or amplify autologous innate stimuli leading to stronger immune responses.

In the CHS model, sensitization can be restored in CHS-resistant TLR4/IL-12Rβ2 mice by heterologous innate stimuli. Their DCs lack sensitizing capacity when injected into the skin of wild-type mice [145]. However,

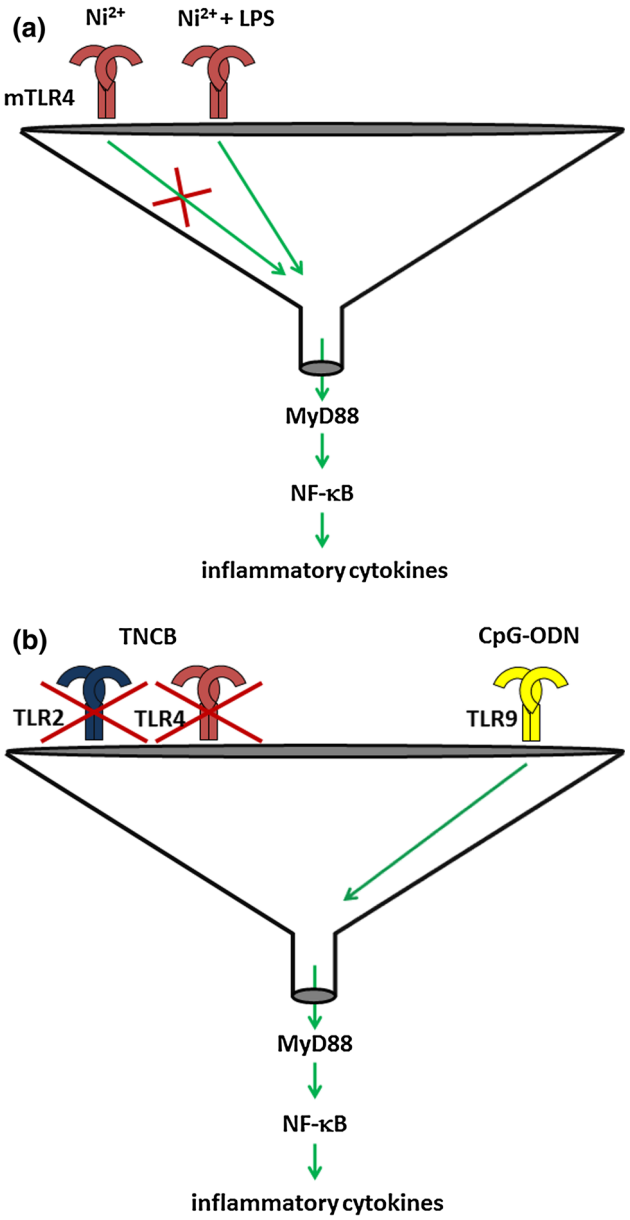

Fig. 5 Loss of resistance to CHS due to heterologous innate immune stimulation. **a** Nickel ions cannot bind to murine TLR4 (mTLR4) and mice are therefore resistant to CHS. Addition of LPS, however, can trigger mTLR4 and provide a heterologous stimulus that renders mice susceptible to Ni^{2+}-induced CHS. **b** Mice lacking TLR2 and TLR4 are resistant to TNCB-induced CHS. Heterologous triggering of TLR9 by CpG-ODN renders these mice susceptible to CHS

heterologous innate stimulation of TLR4/IL-12Rβ2 DCs by in vitro pre-treatment with the TLR9 ligand CpG-oligodeoxynucleotide (CpG-ODN) or by direct skin injection of CpG-ODN into TLR4/IL-12Rβ2 deficient mice prior to epicutaneous sensitization with TNCB (our unpublished data) restored sensitization and CHS. Thus, lack of TLR2/4 signaling or TLR4/IL-12Rβ2 signaling can be compensated by heterologous innate immune stimulation via TLR9 (Fig. 5b). These data illustrate that heterologous innate immune stimulation can overcome genetic resistance to ACD.

The importance of appropriate and sufficient innate immune stimulation is obvious. Activation and full maturation of DCs crucially depends on innate immune stimuli. In the absence of such stimuli or in the presence of insufficient stimulation, DCs may remain immature or semi-mature. If they then present antigens to T cells anergy or Treg can be induced [160–162]. This knowledge is used for the targeting of antigen to immature DCs in the absence of innate stimulation for the induction of tolerance [163, 164]. In the presence of TLR ligands immunity is efficiently induced or enhanced [165]. In the case of contact allergens, the use of sub-sensitizing doses results in low zone tolerance, i.e., antigen presentation to T cells on tolerogenic DCs most likely due to absent or insufficient innate immune stimulation [166]. In this case, heterologous innate immune stimulation might result in the breaking of tolerance (Fig. 2).

These findings also indicate how heterologous innate immune stimulation can be used to manipulate immune responses. Thus, adjuvants can break tolerance while the lack of appropriate innate immune stimulation can result in tolerance. This opens the possibility to use stimulatory or tolerogenic adjuvants or to interfere with innate immune stimulation and, in addition, to exploit adjuvants that impact the T cell polarizing potential of DCs. For example, certain ligands for TLRs, NLRs or CLRs in fact drive DC to induce Th2 responses [167]. Moreover, the strength of the innate stimulus may be varied to achieve tolerization rather than immunity or to control the magnitude of the immune response.

A recent dramatic example for the relevance of heterologous innate immune stimulation was provided for LPS-mediated sepsis. A TLR4-independent, lipid A-mediated non-canonical pathway for caspase-11-dependent activation of the NLRP3 inflammasome and pyroptosis was identified. Intracellular sensing of LPS resulted in pyroptosis. This required priming of the NLRP3 inflammasome via TLR4. In a mouse model, TLR4-deficient mice were resistant to LPS-induced sepsis. However, when priming was performed by heterologous innate immune stimulation using the TLR3 ligand poly I:C, the mice succumbed to TLR4-independent LPS-induced sepsis due to NLRP3-mediated pyroptosis [168, 169]. Thus, co-infections or trauma that produces PAMPs or DAMPs, which trigger other TLRs, can turn resistance into susceptibility. These findings impressively demonstrate the relevance of heterologous innate immune stimulation. They also have potential clinical relevance with respect to therapeutic approaches that solely target TLR4 in septic shock.

As for delayed-type hypersensitivity (type IV allergy) such as ACD, heterologous innate immune stimulation should also be relevant for IgE-mediated immediate-type hypersensitivity (type I allergy) such as rhinitis and asthma. Pollen from many different plant species can cause type I allergies. The reactivity of B cells and T cells is highly specific for distinct epitopes from pollen proteins. As for type IV allergies, innate immune system activation is required for the allergic response. In recent years, it has become clear that pollens are not only allergen carriers but contain lipid mediators, enzymes such as NADPH oxidases and other compounds such as adenosine that can trigger, promote and polarize innate inflammatory responses [170]. Again here, the co-occurrence of different pollen species or pollen in the context of other heterologous innate immune stimulants may lead to the amplification of innate immune responses or the conversion of non-allergenic pollen into allergenic pollen due to heterologous innate immune stimulation based on the uncoupled specificities of the innate and adaptive immune response.

Conclusion

The innate immune system is able to adapt in response to commensals, infection, xenobiotic chemicals and other assaults. Its activation threshold is established in a calibration process that integrates signals from commensal bacteria and most likely from endogenous danger signals. Upon its activation, both innate immune cells and tissue cells may acquire a state of heightened reactivity due to adaptation processes that may be imprinted by epigenetic modifications and lead to trained innate immunity. This (pre-)conditioning of the tissue microenvironment and the context in which a pathogen or a chemical is acting on the immune system crucially influences the quality and quantity of the resulting immune response. Due to individually different immune histories, the thresholds for induction of innate inflammatory and adaptive immune responses may vary individually and over time as a consequence of potentially dynamic calibration and adaptation processes [16, 27]. In addition, individually different tissue- and organ-specific thresholds may be established. These may explain, for example, different organ involvements in patients with adverse reactions to the same drugs. These complexities make predictions of individual risks very difficult unless reliable biomarkers that reflect the current immune status can be identified.

The rather broad specificity of the PRR families and their signaling via common pathways enables heterologous innate immune stimulation. This can significantly impact the outcome of innate and, subsequently, adaptive immune responses in a beneficial or detrimental manner. These design features of the innate immune system help to understand how individual immune experience can shape the immune system and impact future immune responses with regards to quality and quantity, individual immune fitness and susceptibility to diseases.

Possible manipulations of the innate immune system may include the lowering or heightening of activation thresholds to increase responsiveness or prevent hypersensitivity, respectively. Heterologous innate immune stimulation can be used to optimize vaccinations, to amplify or attenuate immune responses, to change the polarization of immune responses and to induce tolerance. Therefore, a more detailed understanding of the mechanisms underlying calibration, trained immunity and heterologous innate immunity is needed. This can be exploited for the prevention and therapy of diseases and the improvement of vaccination strategies.

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