Macrophage memory: Types, Mechanisms, and Its Role in Health and Disease

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Abstract

On the basis of the mechanisms of action and characteristics of immune effects, immunity is generally divided into innate and adaptive immunity. Adaptive immunity is associated with the response to non-self entities and is characterized by high specificity and memory. In contrast, innate immunity is believed to lack memory. However, an increasing number of studies have sought to challenge this traditional immunological dogma and have shown that innate immune cells respond to secondary stimulation more strongly and rapidly than to the primary triggers, thus providing evidence of the immune memory in innate immunity. Macrophages, which are among the most important innate immune cells, can also acquire memory that facilitates the mediation of recall responses. Macrophage memory is a relatively new concept that is revolutionizing our understanding of macrophage biology and immunological memory and could lead to a new class of vaccines and immunotherapies. In this review, we describe the characteristics and mechanisms of macrophage memory, as well as its key roles in various diseases.

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Abbreviations: NK, natural killer; LPS, lipopolysaccharide; BCG, Bacillus Calmette-Guérin; PRR, pattern recognition receptor; PAMPs, pathogen-associated molecular patterns; DAMPs, danger-associated molecular patterns; TLR, toll like receptor; TNF-α, tumor necrosis factor-a; IL, interleukin; H3K4me3, tri-methylation of histone H3 at lysine 4; ox-LDL, oxidized low-density lipoprotein; miRNAs, microRNAs; mTOR, mammalian target of rapamycin; HIF-1α, hypoxia-inducible factor-1α· PIR-A, paired immunoglobulin-like receptor-A; MHC, major histocompatibility complex; TAM, tumor-associated macrophage

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Abstract

On the basis of the mechanisms of action and characteristics of immune effects, immunity is generally divided into innate and adaptive immunity. Adaptive immunity is associated with the response to non-self entities and is characterized by high specificity and memory. In contrast, innate immunity is believed to lack memory. However, an increasing number of studies have sought to challenge this traditional immunological dogma and have shown that innate immune cells respond to secondary stimulation more strongly and rapidly than to the primary triggers, thus providing evidence of the immune memory in innate immunity. Macrophages, which are among the most important innate immune cells, can also acquire memory that facilitates the mediation of recall responses. Macrophage memory is a relatively new concept that is revolutionizing our understanding of macrophage biology and immunological memory and could lead to a new class of vaccines and immunotherapies. In this review, we describe the characteristics and mechanisms of macrophage memory, as well as its key roles in various diseases.

Keywords: macrophage memory; trained immunity; endowed immunity; epigenetic reprogramming

Introduction

Depending on the types of participating cells, recognition patterns, and effector mechanisms, immunity is traditionally divided into two categories, namely, innate and adaptive immunity. The former is mediated by phagocytes, such as monocytes, macrophages, and neutrophils, as well as natural killer cells (NK cells), and is characterized by a rapid and non-specific immune response, whereas the latter is mainly mediated by T and B lymphocytes and is characterized by a slower, albeit highly specific, response. It is generally believed that the immunological memory is associated exclusively with adaptive immunity, and not innate immunity. Nevertheless, it has long been debated as to whether innate immunity also has memory feature, and the recent findings have indeed indicated that immunological memory is not an exclusive hallmark of adaptive immunity [1, 2]. For example, plants and invertebrates, which lack adaptive immunity, are protected against secondary infections, and invertebrates can also exhibit transplant rejection[3-6]. Macrophages, which are key innate immune cell types, participate in innate immunity by phagocytizing foreign bodies, and initiate adaptive immunity by capturing and processing antigens, which are subsequently presented to lymphocytes, thereby playing a central role in immune responses [7, 8]. Moreover, macrophages exhibit certain immune memory-related properties that are traditionally attributed to adaptive T and B cells. However, compared with the memory of adaptive immunity, macrophage memory remains comparatively unknown. Herein, we describe two types of macrophage memory, namely, trained immunity (innate immunological memory) and endowed immunity (adaptive immune-like memory) (Figure 1), as well as the essential roles these play in a range of diseases.

Trained immunity (innate immune memory)

In 2011, Netea et al. [3] first proposed the concept of "trained immunity" to describe the ability of mammalian innate immunity to exhibit immune memory, monocytes/macrophages, NK cells, and granulocytes that show altered immune responses to secondary stimulation originating from exogenous or endogenous insults. In terms of cell populations and molecular mechanisms, there are important differences between trained immunity and classic adaptive immune memory. While adaptive immune memory generally implies high specificity and cascade amplification, trained immunity is a non-specific or semi-specific phenomenon that is mainly characterized by alterations in the number and/or function of innate immune cells, and subsequently involves

the initiation of a pro-inflammatory or anti-inflammatory secondary immune response [3, 9, 10]. Depending on the nature and the dose of the primary stimulus, trained immunity responds to the secondary challenge via one of two contrasting functional programs, with enhanced immunological imprinting being manifested as training, and the suppressed program contributing to tolerance [10, 11].

Discovery and characteristics of trained immunity

Freudenberg et al. [12] reported that in mice, macrophages primarily stimulated by sepsis or high-dose lipopolysaccharide (LPS) induce immune tolerance and exhibit a suppressed immune response to avoid the development of a state of excessive inflammation on secondary challenge. Quintin et al.[13] also showed that whereas macrophages can be trained by β-glucan (the main cell wall structural component of the yeast*Candida albicans*), mice lacking functional T and B lymphocytes are protected against reinfection of multiple pathogens such as *C. albicans* and *Staphylococcus aureus* . Indeed, increasing number of studies have indicated that bacterial, fungal, parasitic, and viral infections can train monocytes/macrophages to promote the secretion of inflammatory cytokines and enhance phagocytosis in response to secondary stimulation, thereby confirming the universality of macrophage memory[13-17]. In addition to studies using animal models, a study on childhood vaccination reported that the Bacillus Calmette-Guérin (BCG) vaccination can enhance the defense against infections other than those caused by mycobacteria in a monocyte-dependent manner, thereby leading to an overall reduction in child mortality [18]. Furthermore, accumulating epidemiological data indicates that live vaccines, such as the measles, smallpox, and polio vaccines, provide non-specific protective effects against a broad range of infections other than those caused by the respective target viruses [19-22].

These studies have revealed two important characteristics of trained immunity. Firstly, trained immunity is a non-specific or semi-specific phenomenon, with its specificity being lower than that of adaptive immunity; and as such, it can provide cross-protection against a wide range of pathogens. Secondly, trained immunity primarily stimulated by infections or vaccines induces a pro-inflammatory or anti-inflammatory secondary immune response independent of classical T/B cell adaptive immunity.

Mechanisms of trained immunity

Unlike the classical adaptive immune memory, which is dependent on antigen-specific gene rearrangement, the mechanisms underlying trained immunity mainly include altered pattern recognition receptor (PRR) expression, epigenetic reprogramming, and metabolic reprogramming. Moreover, these mechanisms may be characterized by a degree of synergism, rather than functioning completely independently.

Altered pattern recognition receptor expression

In response to a primary challenge, macrophages acquire an immune memory phenotype and upregulate PRR expression to promote the recognition of diverse foreign antigen-derived pathogen-associated molecular patterns (PAMPs) and self-derived danger-associated molecular patterns (DAMPs), and subsequently produce an altered immune memory response[23-25]. Following stimulation by different PRR ligands such as the dectin-1 ligand β-glucan, Toll like receptor 2 (TLR2) ligand lipoteichoic acid, TLR4 ligand LPS, and nucleotide-binding oligomerization domain-containing protein 2 (NOD2) ligand muramyl dipeptide, monocytes/macrophages modify the secretion of pro-inflammatory cytokines tumor necrosis factor-a (TNF-α) and interleukin (IL)-6, and initiate an altered immune response on secondary encounter [26]. In addition, the macrophage memory induced by cell surface receptors may be retained following cell differentiation. The findings of a recent study have revealed that macrophages derived from mice or human hematopoietic stem and progenitor cell subsets that are exposed to a TLR2 agonist prior to or during macrophages differentiation, develop immune tolerance during the secondary response and produce lower levels of the inflammatory cytokines TNF-α, IL-6, and IL-1β [27].

Epigenetic reprogramming

Epigenetic reprogramming of innate immune cells is among the most important mechanisms associated with trained immunity. Epigenetic reprogramming involves multiple mechanisms, among which histone modification plays a key role in the induction of macrophage memory.

In the case of *Candida* infections, monocytes/macrophage memory trained by β-glucan has been found to be associated with epigenetic changes involving the enhanced tri-methylation of histone H3 at lysine 4 (H3K4me3) [13]. In addition, in vitro stimulation of human monocytes with oxidized low-density lipoprotein (ox-LDL) has been observed to promote H3K4me3 and the upregulated expression of different inflammatory cytokines associated with atherosclerosis, including IL-6, IL-8, IL-18, and TNF-α [28]. On the basis of inflammatory status (the expression of pro-inflammatory mediators, such as TNF-α and IL-6), LPS exposure and β- glucan priming have been shown to induce distinct functional programs of macrophage memory, namely, tolerance and training. The contrasting functional changes in macrophages are associated with specific epigenetic changes such as H3K4me1 and H3K27ac. However, whereas H3K27ac, which marks active promoters and enhancers, is a dynamic modification that gradually disappears after the stimulation subsided, the distal regulatory element (enhancer) marker H3K4me1 remains accessible [11]. In conclusion, H3K4me1 may serve as a marker that contributes to maintaining the immunological memory of macrophages.

Additionally, when macrophages are stimulated with low-dose LPS, latent enhancers that are normally inactive, label-free, and unbound by transcription factors are selectively activated and acquired H3K4me1 marks after the resolution of stimulation, and once having been unveiled, the histone marks persist and mediate a stronger pro-inflammatory response upon subsequent stimulation[29]. Whereas monocytes/macrophages can be stimulated in response to high-dose LPS, the induction of macrophage memory involves H3K9me2 and H3K27me2 modification [30]. Kleinnijenhuis et al. [31] have also reported that TLR4-NOD2 is involved in the protective effect of monocytes against secondary reinfection after primary BCG vaccination in healthy volunteers. The enhanced function of monocytes in this case was found to be mediated by H3K4me3, with the production of the inflammatory cytokines IFN-γ, TNF, and IL-1β increasing several-fold in response to infections by non-specific bacterial and fungal pathogens. Moreover, the inhibition of histone methyltransferase was found to be associated with a significant reduction in BCG-induced macrophage memory.

Further factors that play important roles in the induction of macrophage memory are microRNAs (miRNAs), which serve as key regulators of immune cell development and function [32]. In this regard, Seeley et al. [33] have reported that prolonged exposure to LPS in mice led to an increase in the expression of miRNA-221 and miRNA-222, followed by transcriptional silencing of certain inflammatory genes through switch/sucrose non-fermentable (SWI/SNF) and signal transducer and activator of transcription (STAT)-mediated chromatin remodeling. This in turn was found to promote immune tolerance to secondary challenge, thereby indicating the regulatory effects of miRNAs in the functional reprogramming of macrophage memory. An enhancement in the expression of miRNA-221 and miRNA-222 has also been established to be associated with immunoparalysis and heightened organ damage in patients with sepsis. In addition to miRNAs, it is conceivable that long non-coding RNAs (lncRNAs) also play roles in macrophage memory. Indeed, Fanucchi et al. [34] found that the newly identified immune gene initiation lncRNA (IPL) directed WD repeat-containing protein 5 (WDR5)-mixed lineage leukemia protein 1 (MLL1) histone methyltransferase complex formation and subsequent H3K4me3 accumulation on the promoters of IL-6, IL-8, and CXCL1, thereby resulting in a stronger inflammatory response in β-glucan-induced trained immunity.

Metabolic reprogramming

Trained immunity has also been established to involve changes in cell metabolism, as indicted by the different metabolic pathways of two types of activated macrophage, namely the classically activated M1 macrophages and alternatively activated M2 macrophages. Whereas M1 macrophages tend to utilize glycolytic metabolism for energy generation, M2 macrophages are primarily dependent on oxidative phosphorylation for ATP biogenesis[35, 36]. In this context, Cheng et al.[37] have reported that the metabolic basis of trained immunity triggered by the*C. albicans* cell wall constituent β-glucan is the induction of aerobic glycolysis dependent on an AKT-mammalian target of rapamycin (mTOR)-hypoxia-inducible factor-1α (HIF-1α) pathway. Furthermore, trained human monocytes have been shown to be characterized by high glucose consumption, high lactate production, and a high ratio of nicotinamide adenine dinucleotide (NAD^+) to nicotinamide adenine dinucleotide (NADH), reflecting a shift in cell metabolism from oxidative phosphorylation to aerobic glycolysis. Similar changes in glucose metabolism have also been observed in BCG-induced trained immunity [38].

Such changes in cell metabolism facilitate the rapid conversion of glucose to lactic acid in the cytoplasm, thereby yielding the energy necessary to mount a rapid response to secondary challenge [39]. Furthermore, in the case of LPS-induced immunological memory, macrophages have been observed to display strong and transient glycolytic metabolism during the acute response, whereas after the stimulation subsided, the metabolic polarity shifts back to oxidative phosphorylation, and histones in the transcriptional region of the genome are deacetylated by deacetylase-1 and deacetylase-6, thereby establishing the immune tolerance memory of macrophages[40]. In addition, intermediate metabolites have also been established to be involved in the regulation of macrophage memory. For example, the metabolite mevalonate has been shown to induce trained immunity by activating IGF1-R and mTOR and subsequent histone modifications in inflammatory pathways [41]. Furthermore, the tricarboxylic acid cycle (TCA) metabolite fumarate provides a link integrating immune and metabolic circuits to induce the epigenetic reprogramming of monocytes by downregulating KDM5 histone demethylases [42, 43]. Additionally, glutamine metabolism has been demonstrated to promote a high accumulation of α-ketoglutarate, and a corresponding elevation in the α-ketoglutarate/succinate ratio was found to be sufficient to regulate H3K27me3 modification and ten-eleven translocation-dependent DNA demethylation, which contribute to the induction of macrophage memory[42-44].

Endowed immunity (adaptive immune-like memory)

Studies on transplant rejection provide a fundamental basis for challenging the assumption that innate immune cells acquire immune memory independent of adaptive immunity. In endowed immunity, macrophages are endowed with adaptive immune-like memory that facilitates the recall of primary immune responses. However, high-specificity endowed immunity responses to secondary stimuli necessitate the assistance of helper T cells [45].

Discovery and characteristics of endowed immunity

Dai et al. [46] showed that mice monocytes/macrophages can acquire an alloantigen-specific memory in response to secondary encounters, and identified that paired immunoglobulin-like receptor-A (PIR-A), a major histocompatibility complex (MHC)-I receptor, was necessary for the induction of macrophage memory. Either deleting PIR-A or blocking the PIR-A-MHC-I combination was demonstrated to suppress memory and attenuate the allograft rejection in kidney and heart transplantation. Similarly, Liu et al. [47] have reported that during secondary challenge, macrophages have the capacity to recognize and reject allogeneic antigens, which requires two signals, namely, priming with allogeneic antigens and the assistance of $CD4^+$T cells. Chu et al. [48] also showed that macrophages primed with allogeneic antigens mounted an acute response to skin allografts with a certain degree of antigen specificity, which is similar to the characteristics of adaptive immune cells. The authors demonstrated that immunodeficient recipient mice showed no signs of rejection to allogeneic skin grafts, which is consistent with the findings of previous studies that have established that innate immune cells alone are insufficient to facilitate the rejection of allogeneic organ grafts. However, they found that immunodeficient recipient mice, which received antigen-immunized macrophages (primed macrophages) from immunocompetent mice, were able to efficiently reject the same allogeneic skin grafts, although not third-party skin grafts, or showed significantly slower rejections of the grafts. In summary, when primed macrophages in immunocompetent mice are exposed to the same allogeneic antigen secondarily, primed macrophages undergo pronounced proliferation, expand during the immune response and exert a direct graft-rejection effect, at least partially, via a perforin-dependent pathway.

In addition, the assistance of helper $CD4^+$T cells, but not $CD8^+$T cells, during the priming period was found to be essential for naïve macrophages to gain the ability to distinguish allografts and thus promote rejection [48-50]. In a follow-up study, the same authors reported that the specific memory of primed macrophages in the rejection of allogeneic cells and skin grafts was long-term and persisted for at least 4 months (until the end of the experimental period) [51]. In conclusion, macrophages can become endowed with memory that facilitates the recognition of allogeneic antigens or specific molecules, and thereby induce an inflammatory response on secondary encounter. Accordingly, suppressing this memory may represent a potential therapeutic strategy for improving transplantation outcomes. However, in a study of mouse alveolar macrophages, Yao et al. [52] found that the induction of macrophage memory after respiratory viral infection required the assistance of

effector $CD8^+$ T cells, but not $CD4^+$ T cells.

Taken together, the findings of the aforementioned studies indicate that functional endowed immunity may require the assistance of different types of T cells in different disease models. Hence, further studies are needed to determine which T cell subsets facilitate the induction of macrophage memory under different conditions. Although endowed immunity may be associated with the secretion of inflammatory effectors and amplified adaptive immune responses [45, 53], the precise nature of the underlying molecular mechanisms remain unclear and necessitate further study.

The essential role of macrophage memory in disease responses

Macrophage memory is closely associated with various diseases. As a novel strategy for diseases prevention and treatment, macrophage memory is beneficial for promoting host immune response against infections. In contrast, this type of memory may be maladaptive or potentially detrimental in the context of transplant rejection or immune-mediated and chronic inflammatory diseases, such as rheumatoid arthritis and atherosclerosis [10, 54, 55].

Infections

In a mouse model of recurrent skin and skin structure infections, macrophage memory reduced the severity of skin damage and promote an increase in the production of cytokines associated with skin protection and prevention of dissemination. Furthermore, the adoptive transfer of trained macrophages into naïve skin has also been established to afford protective efficacy [56]. In addition, trained macrophages of mice that had previously been infected with*S. aureus* , have been observed to be associated with more rapid monocyte recruitment, enhanced bactericidal effects, improved healing, and the enhanced resistance of these mice to secondary infections [57].

Atherosclerosis

In addition to microbial products, endogenous non-microbial stimulus ox-LDL and lipoprotein (a) also induce monocyte/macrophage immune memory and play important roles at different stages of atherosclerosis[28, 58]. In this context, trained human monocytes have been found to switch to an enduring pro-atherogenic macrophage phenotype via epigenetic histone modifications associated with the downregulation of H3K4me3 on the promoters of pro-inflammatory cytokines and a metabolic shift toward increased glycolysis. When stimulated secondarily by TLR2 and TLR4 ligands, there is a substantial increase in the production of pro-atherogenic factors, such as TNF-α, IL-1β, IL-6, and monocyte chemoattractant protein-1 (MCP-1), which may lead to arteriosclerotic plaque instability and exacerbate atherosclerosis[28, 59-61].

Inflammatory diseases

A distinctive feature of inflammatory diseases, IL-1β also serves as an inducer of immunological memory. For example, it has been demonstrated that IL-1β pre-treatment protects mice against lethal *Pseudomonas*infection, and has also been reported to mediate the immune response in human BCG vaccination, thereby indicating that this cytokine may play an important role in the macrophage memory associated with inflammatory diseases [62-64]. This supposition in indeed supported by the fact that β-glucan-induced macrophage memory can contribute to inhibiting IL-1β-mediated inflammation. β-glucan is recognized as a classical immune memory inducer that can also activate NOD-, LRR-, and pyrin domain-containing protein 3 (NLRP3) inflammasome, the biochemical function of which is to activate cysteine-requiring aspartate proteinase-1 (caspase-1) and subsequent IL-1β production, thereby establishing macrophage memory and a marked attenuation of IL-1β secretion in NLRP3-associated inflammatory diseases [65, 66].

Cancer

Immunological memory has also been established to play a central role in tumor progression. For example, β-glucan-induced mouse granulocyte immune memory is reportedly associated with diminished tumor growth, with this anti-tumor effect being attributed to a reprogramming of neutrophils toward an anti-tumor phenotype, a process dependent on type I interferon signaling, although independent of host adaptive

immunity[67]. Indeed, innate immune cells may play opposing roles by displaying both tumor-suppressing and tumor-promoting properties. For example, in terms of suppression, BCG treatment has long been known to eradicate malignancies such as bladder cancer and melanoma and reduce the risk of leukemia and lymphoma [68-71]. Furthermore, β-glucan has also been used in clinical trials for cancer therapy such as that for non-small cell lung, breast, and colorectal cancers [72]. The findings of further studies have revealed that such anti-tumor effects may be attributable to the non-specific protection triggered by epigenetic reprogramming and is associated with the induction of monocyte/macrophage memory[31, 73].

With respect to the tumor-promoting effects of macrophage memory, tumor-associated macrophage (TAM), which serves as important immune regulatory element in tumor progression, has been shown to be involved in the development of an immunosuppressive tumor microenvironment and facilitate tumor immune escape, growth, and metastasis[74, 75]. The salient feature of TAM differentiation is epigenetic reprogramming involving histone modification, such as H3K4me3 and H3K9me3 alterations in the promoter regions of IL-6 and TNF-α, thereby inducing the production of pro-inflammatory cytokines and expression of tumor-associated gene profiles [76]. For example, predominant functional changes in thyroid cancer (TC)-induced macrophage memory enhance inflammatory properties and the modification of cell metabolism. This functional reprogramming has been established to be partially mediated by TC-derived lactate via AKT1/mTOR-dependent aerobic glycolysis, resulting in long-term epigenetic modifications at histone methylation levels, such as H3K4me3 and H3K9me3 in the promoters of IL-6 and TNF-α, thereby leading to increases in the expression of genes characteristic of cancer tumor profiles, and an increase in the production of TAM pro-inflammatory factors [76, 77].

Other diseases

Human and mouse macrophages trained by low-dose LPS attenuate the inflammatory phenotype of endometriotic cells via an IL-10-dependent pathway, and significantly upregulated H3K4me3 on the IL-10 promoter and altered inflammatory cytokine production have been observed simultaneously in endometriosis [78]. In addition, evidence of macrophage memory has also been obtained with respect neurodegenerative disorders, such as Alzheimer's disease, Parkinson's disease, and autism spectrum disorder [55]. In a mouse model of Alzheimer's pathology, LPS-induced immune training has been demonstrated to exacerbate cerebral β-amyloidosis, whereas this could be alleviated by immune tolerance, attributable to microglial (brain-resident macrophage) memory, along with altered inflammatory cytokine production and H3K4me1 and H3K27ac enrichment[79]. Furthermore, in respiratory diseases such as allergic asthma, allergen-triggered macrophages have been observed to acquire a TNF-dependent inflammatory memory and show an excessive mediator response upon stimulation, thereby resulting in a shift toward an M2-like macrophage phenotype and the production of diverse inflammatory cytokines. Conversely, TNF blockade or genetic ablation has been found to prevent the inflammatory imprinting of macrophages[80]. The concept of macrophage memory presents a new perspective for better understanding of disease pathology, and elucidating the precise underlying mechanisms may provide relevant insights for the development of novel therapeutic strategies.

Conclusion & perspectives

Trained or primed macrophages exhibit immune memory similar to that of adaptive immunity when challenged with secondary triggers. There are two types of macrophage memory, namely, trained and endowed immunity. Trained macrophages acquire memory via epigenetic and metabolic reprogramming, induce trained immunity, and facilitate an altered immune response upon secondary stimulation. Similarly, primed macrophages can acquire memory, which leads to the development of endowed immunity and allogeneic rejection in response to stimulation with the same allogeneic antigen. The discovery of macrophage memory has challenged traditional dogma regarding the limitations of immunological memory and enriched our understanding of macrophage-mediated immune responses. More importantly, unraveling macrophage memory provides a more comprehensive perspective on the pathogenesis of immune-mediated diseases, and may lead to establishing a new class of vaccines and the development of novel immunoprophylactic and therapeutic strategies.

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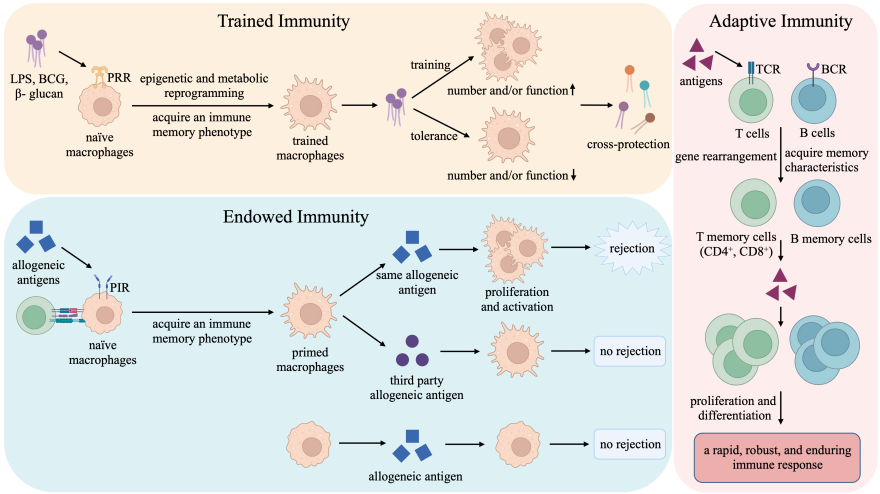
Figure legend

Figure 1 . There are two types of macrophage memory: trained and endowed immunity. In trained immunity, macrophages acquire an immune memory phenotype via epigenetic and metabolic reprogramming and exhibit an enhanced (training) or suppressed (tolerance) host defense response toward a secondary challenge. In endowed immunity, macrophages primed by allogeneic antigens acquire the potential ability to reject allogeneic grafts bearing the same antigen, with the assistance of helper $CD4^+$ T cells, although lack the capacity to reject third-party grafts. In adaptive immunity, T and B cells display a highly specific immune memory subsequent to primary exposure to antigens and produce a rapid, robust, and enduring immune response.



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