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Innate Immune Memory in Macrophages

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Abstract

Macrophages have been recognized as the primary mediators of innate immunity starting from embryonic/fetal development. Macrophage-mediated defenses may not be as antigen-specific as adaptive immunity, but increasing information suggests that these responses do strengthen with repeated immunological triggers. The concept of innate memory in macrophages has been described as “trained immunity” or “innate immune memory (IIM).” As currently understood, this cellular memory is rooted in epigenetic and metabolic reprogramming. The recognition of IIM may be particularly important in the fetus and the young neonate who are yet to develop protective levels of adaptive immunity, and could even be of preventive/therapeutic importance in many disorders. There may also be a possibility of therapeutic enhancement with targeted vaccination. This article presents a review of the properties, mechanisms, and possible clinical significance of macrophage-mediated IIM.

Keywords

Chromatin; Development; Fetus; Fumarate; Lipoprotein(a); MMP-2; MMP-9; Neonate; Newborn; Succinic acid; α-ketoglutaric acid

Introduction

Macrophages are viewed as key sentinels in the innate immune system throughout the body that contribute to both homeostasis and disease.[1–4] These cells identify, phagocytose, and eliminate invading pathogens; ensure the timeliness of defense reactions by secreting antimicrobial peptides, cytokines to recruit and activate leukocyte present in the vicinity, chemokines to recruit leukocytes from the circulation and other tissues; and promote the resolution of inflammation prior to the onset of illness and by eliminating the pathogens and severely-damaged cells.[1,5–17] These cells also coordinate immune activation by presenting antigens to adaptive immune cells.[18–20]

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Macrophages play a crucial role in immune responses in neonates and young infants, who are yet to acquire protective levels of neutrophil function and adaptive immunity. These cells begin to resemble adult macrophages in many host defense functions by the late 2nd trimester, and are therefore likely to be important even in premature infants. However, macrophages have been studied mostly in the context of innate immunity, not as carriers of immune memory that could enhance the efficiency of elimination of pathogens.[21–23] But now, this perception is changing.[23–26] Preclinical and clinical data indicate that macrophages do retain some memory of previous encounters through epigenetic reprograming and show quicker and more robust responses in secondary infections.[21,23,27–34] This progressive enhancement in macrophage-mediated defenses has been described as "trained immunity" or "innate immune memory (IIM)".[23,32,35,36] Innate immune memory can activate circulating macrophages and those located in the lungs, and suppress many in the intestine.[23,37]

This immunological memory of macrophages may constitute one of five patterns where immune cells learn to mount quicker and enhanced responses to "known" antigens[38,39] (Fig. 1): (1) systemic acquired resistance seen in plants;[40,41] (2) transgenerational immune priming,[42,43] which may include vertical transmission of immune experience from parents to the offspring; horizontal transfer between individuals, and between individuals and other parents' offspring; (3) natural killer (NK)-cell immune memory;[44,45] (4) classical adaptive memory in vertebrates;[46,47] and finally, the increasingly appreciated (5) IIM in myeloid cells (monocytes, macrophages, and dendritic cells).[23,30] In this article, we have focused on the IIM macrophages with a particular focus on the relevance of these cells in the fetus and newborn infants. The dendritic and adaptive immune cells are still evolving in the fetus and neonates,[48] and so we did not include these details in the present article. We included information from some of our own preliminary studies with an extensive literature search in EMBASE, PubMed, and Scopus.[49] To avoid bias in identification of studies, keywords were short-listed *a priori* from PubMed's Medical Subject Heading (MeSH) thesaurus.[50]

Development of Macrophages in the Fetus and Neonate

All tissues contain a complement of yolk sac (YS), hepatic, and bone marrow-derived macrophages.[2,51] The numbers are considerable in many tissues and may reach 5,000–10,000 per cubic mL.[23,52] During evolution, macrophages appeared earlier than the lymphocytes known for classical immune memory (details in Mezu-Ndubuisi and Maheshwari).[1] The following graphic (Fig. 2) shows the three major pathways of macrophage differentiation; the terminal stages of development with noted findings of IIM have been highlighted in each pathway:

- **Macrophage differentiation from lineage-restricted YS progenitors:** Hemocytoblasts resembling myeloblasts are first seen in the secondary YS (Fig. 2A) on day 18.[53] On day 19, some hemocytoblasts differentiate directly into embryonic macrophages.[54] During the days 25–30, many erythro-myeloid progenitors (EMPs) also differentiate into macrophages.[55] Around this time, some hematopoietic stem cell (HSC) clusters of differentiation (CD) 45 and 34 ($CD45^+$ $CD34^+$) migrate from the peri-aortic region to the central nervous system (CNS) and differentiate into microglia.[56]

- **Macrophage differentiation in the aorta-gonad-mesonephros (AGM) zone:** The vascular endothelium here (Fig. 2B) produces CD45$^+$ CD34$^+$ HSCs,[57] which can differentiate first into common myeloid progenitors (CMPs) and then into tissue macrophages. These macrophages migrate to all the embryonic organs except the CNS. These cells express characteristic markers such as the angiotensin-converting enzyme, T-cell acute lymphocytic leukemia 1/stem cell leukemia (Tal/SCL) gene, and the myeloblastosis oncogene (c-Myb).[58]

- **Macrophage differentiation in the liver and the bone marrow:** On day 32, the CD45$^+$ CD34$^+$ HSC precursors of macrophages migrate from the AGM zone to the liver and the bone marrow (Fig. 2C).[59] Some of these cells may arise from EMPs. Hepatic HSCs are known to differentiate into monocytes and macrophage precursors between 8 and 20 weeks' gestation and then involute during the 20–23 weeks period. After birth, the hepatic HSCs migrate to the bone marrow for further definitive hematopoiesis.

  Increasing information suggests that most tissue macrophages, even in adults, likely originate from the EMP and AGM progenitors acquired during embryonic development, not from circulating monocytes.[2,59,60] However, the ontogeny of monocyte-derived macrophages (MDMs) is best lineated in marrow-derived monocytes. CD45$^+$ CD34$^+$ HSCs in the bone marrow clearly differentiate into CMPs, granulocyte-monocyte precursors (GMPs), common monocyte and DC precursors (MDPs), pre-monocytes (committed monocyte progenitors), monocytes, and then into macrophage precursors by the 7th week of gestation.[61] These hematopoietic lineages can be detected in other tissues such as the brain, heart, liver, and skeletal muscle.

  In the bone marrow, more than 90% of HSCs differentiate into classical monocytes with strong CD14 expression (CD14^{++}). These cells mature into M1 macrophages that strongly react to toll-like receptor (TLR) ligands, and express inflammatory cytokines and reactive oxygen species (ROS). About 10% develop into a nonclassical, CD16^{++} subset. These cells produce some inflammatory cytokines, but not much ROS. These cells patrol and assess endothelial integrity and infiltrate normal tissues.[62] A third, intermediate CD14$^+$ CD14$^+$ population may show both inflammatory and tissue healing properties; these cells may express MHC-II, show strong phagocytic activity, present antigens, and contribute to T-lymphocyte activation.[62]

In premature and young infants, macrophages show developmental changes in antigenic profiles. These cells express high levels of CD11b, chemokine receptors CCR1, CCR2, CCR5, CXCR1, CXCR2, and other molecules such as CD115, glycan structures containing 6-sulfo *N*-acetyl lactosamine, and triggering receptors expressed on myeloid cells (TREM) are high. There might be some immaturity in movement, phagocytosis, and regulation of inflammation. These cells can be stimulated by many endogenous triggers such as cytokines; oxidized lipids; ROS and reactive nitrogen species (RNS); metabolic products, and débris released from dying cells such as heat-shock proteins (HSPs) and damage-associated molecular patterns (DAMPs).[63] There are also multiple well-known exogenous activators such as microbial products, microparticles, and chemicals.[63]

Innate Immune Memory in Neonatal Macrophages

Increasing information indicates that macrophages do retain some memory of previous encounters and show quicker, more robust responses in secondary infections (Fig. 3). This immunological memory very likely enhanced the survival of early multicellular eukaryotes by enhancing the defense responses.[31] Innate immune memory macrophages may not fit in the current dualistic model of classic (M1) or alternative (M2) macrophage polarization, and may need to be classified in a distinct category (Fig. 4, Table 1). There is increased expression of CD43 and CD206, but other surface markers can differ in specific model(s). In mice treated with Bacillus Calmette-Guérin (BCG), peritoneal macrophages showed enhanced expression of CD43, CD206, CCR2, CXCR4, CD80, and TLR2.[64] Low doses of lipopolysaccharide (LPS) induced an overlapping profile with increased CD206 and CD43, but less CCR2, CXCR4, and CD80. Innate immune memory macrophages also show a shift toward increased glycolysis and altered energy metabolism.[32,65,66]

Macrophages recognize most antigens through the pattern recognition receptors (PRRs) expressed on the cell surface. These receptors can recognize pathogen-associated molecular patterns (PAMPs) in structural débris or secreted products. Some PRRs can identify DAMPs, the endogenous danger signals expressed on or released from dying cells.[67] Pathogen-associated molecular patterns are important for microbial survival and have been evolutionarily conserved with minimal diversification.[68] The best-known examples are LPS and porins of Gram-negative bacteria; peptidoglycans of Gram-positive bacteria; flagellins; β-glucans and mannans from fungi; and bacterial and viral nucleic acids.[69–76] The specificity for classes, not individual microbes, has helped in evaluation of molecular dynamics in pathogens. Damage-associated molecular patterns can be seen in intracellular proteins such as the HSPs and the high-mobility group box 1 (HMGB1); extracellular matrix components such as hyaluronan fragments; and non-protein components such as adenosine triphosphate (ATP), uric acid, heparin sulfate, and deoxyribonucleic acid (DNA).[77]

The traditional view of macrophage function as limited to the first line of defense may indeed be too restrictive.[6] However, macrophage IIM is still less robust than the classical adaptive memory of T- and B-lymphocytes.[31] Despite all possible differences in ontogeny and genetic expression (as noted in epigenomic or transcriptome profiles), there are notable similarities in functional responses to immunological challenges. The consistency of these responses, the context, the microenvironmental cytokine *milieu*, and the evidence supporting stimulus memory suggest a possibility of convergent evolution.[20,78,79] These host-defense responses may not be as perfectly antigen specific as in lymphocytes, but these do seem to gain in efficiency with repeated exposures.[23,35,36,79] Innate immune memory seems to alter inflammatory responses more than its effects on phagocytosis and other motor activities.[28,80]

Increasing evidence suggests that immune memory may include a full spectrum of responses ranging from the IMM seen in macrophages to the classical adaptive immune memory of lymphocytes. When re-exposed to defined stimuli, other leukocytes such as the B-1 and marginal zone B-cells, invariant NK, innate lymphoid cells, and γδ T-cells also show some enhancement of secondary responses. However, these responses are not as consistent as in myeloid cells (Table 2).[31,81,82] The differences between IIM and classical immune memory of lymphocytes are more clearly noticeable. Upon antigen exposure, naïve lymphocytes undergo genetic rearrangements and evolve into specific, mature clones with increased sensitivity to the original antigens.[83,84] These mature lymphocytes, in turn, can recruit more naïve lymphocytes to differentiate into the needed clones and thereby establish feedforward loops.[85] Most lymphocytes become effector cells that provide host defense, but some evolve into longer-living memory cells.[86] If exposed to the same antigen at a later time-point, the memory cells proliferate to form large pools of effector and memory cells. Some memory T-cells can also transgress into effector cells.[87]

Macrophage IIM is largely mediated via epigenetic changes, and its kinetics differs from that of lymphocyte-mediated adaptive immunity.[88] Sensitized macrophages display a rapid, potentiated activation following secondary exposures to the same or similar antigens.[89,90] These responses are typically last only for a few weeks to months, and may either be systemic or limited to just the tissue of origin.[35] In contrast, the adaptive immune memory seen in lymphocytes may last for the lifetime of the cells or even that of the organism as it is rooted in genetic mutations, antigen-specific gene rearrangements, and recombinations.[23,84,91] Some of these changes show developmental changes, and further work is needed to understand the functional and clinical importance of macrophage-mediated vs. adaptive immune memory at various stages of fetal/neonatal development.[1]

Macrophage PRRs may be important in immune memory.[89] Administration of BCG might be detected by intracellular PRRs such as the nucleotide-binding oligomerization domain 2 (NOD2), which may protect these cells against secondary infections.[87,92] Nucleotide-binding oligomerization domains are germline-encoded receptors that respond to microbial danger signals.[93,94] These belong in the broader category of conserved cytosolic PRRs, the so-called *NOD*-like receptors (NLRs). Nucleotide-binding oligomerization domains-like receptors sense microbe-associated molecular patterns (MAMPs) during viral and bacterial infections.[95–97] These receptors can sense that MAMPs in the cytoplasm and occasionally in the extracellular space, especially if virulence factors such as muropeptides are transported into the cytoplasm.[98,99] Upon ligand binding, NLRs oligomerize and recruit adaptor proteins to form the so-called inflammasomes, which can activate the production of inflammatory cytokines, antimicrobial peptides, and in some cases, precipitate cell death.[100,101]

Macrophages previously exposed to PRRs ligands, such as dectin-1 ligand, β-glucan, NOD2 ligand muramyl dipeptide, and flagellin show memory and express more tumor necrosis factor (TNF) and interleukin (IL)-6 on secondary stimulation.[102–108] In some conditions, LPS and flagellin can also induce long-term tolerance with less intense inflammatory responses,[109–111] although such tolerance may not always be detectable in premature and critically ill neonates.[1,14,15,112–114] The expression of IIM mediators does not change with cell differentiation, except perhaps for decreased production of TLR2 in specific subsets.[23,115]

Types of IIM in Macrophages

Innate immune memory macrophages show rapid appearance at the sites of infection, phenotypic plasticity, and the ability to sample the inflammatory environment.[28] Changes in surface markers such as the PAMPs and DAMPs may alter function/phenotype of these macrophages in complex and context-specific ways.[68]

Macrophage IIM seems to be comprised of multiple steps. After an initial stimulus primes the inflammatory response, a second one can result either in training and potentiation, or in tolerance (Fig. 5). The details of these training and tolerance responses are provided below:

1. Training: Low doses of bacterial LPS from Gram-negative bacteria, β-glucans from the *Candida albicans* cell wall, and certain parasites and viruses can sensitize macrophages to show enhanced inflammatory responses to secondary infections with many pathogenic bacteria and *Candida* spp.[116–118] Such “training” increased expression of inflammatory cytokines such as TNF and IL-1, IL-6, ROS, and various other cytokines and chemokines. Macrophage training may enhance tissue damage in acute infections, but improves host defense and survival. In mice lacking T- and B-cells, *Candida* infections can prevent repeated infections with pathogenic bacteria.[119] In other studies, administration of the BCG to simulate vaccination can expanded the pool of IIM macrophages with H3K4me3.[119–121]
2. Tolerance: Repeated exposure to high doses of LPS can dampen the inflammatory responses to later encounters with these bacteria, particularly on mucosal surfaces in the gastrointestinal tract.[122–124] Prior infections with the influenza or respiratory syncytial viruses can promote immune tolerance lasting weeks to months to subsequent bacterial infections of the lungs. These viruses desensitize TLRs, particularly TLR5, and the lectin and mannose receptors. It also inhibits NF-κB signaling in alveolar macrophages (AMs), resulting in lower levels of inflammatory factors TNF and IL-17 following exposure to bacterial pathogens. Interferon (IFN)-α/β, IFN-γ, and IL-10 produced during viral infection can further suppress antibacterial resistance by inhibiting the production of free oxygen radicals.[125–128] This tolerance memory in macrophages may be related to a few epigenetically-active histone tags on the promoters and enhancers of antibacterial resistance genes. Interestingly, β-glucan can reinstate cytokine production and partially reverse macrophage immune tolerance by reinstatement of the histone tags.[129]

Epigenetic Changes that Promote Priming in Macrophages

The origin of macrophage IIM is still being investigated, but it is generally visualized as a pattern of consistent, progressively quicker phenotypic shifts in these cells following repeated exposures to specific environmental stimuli.[130–132] Transgenerational memories might require genomic changes, whereas moderate-term memories could be generated by changing the number of cells available to produce a response or by epigenetic modification of the programing of existing cells.[3,43,133] Short-term memories could be generated by the ephemeral changes that are transient, but show diverse concentrations or molecular modifications of signaling components.[109] Taken together, the medium-term duration of IIM of macrophages has brought the focus on epigenetics (Table 3).

Many epigenetic changes in macrophages have been identified as altering the heritable “memory” with specific changes in the three-dimensional structure and compaction of the daughter macrophages. There are at least three categories of such changes: (1) DNA methylation; (2) histone modifications; and (3) regulation of gene expression by non-coding RNAs.[27] The timing of these epigenetic changes in macrophages during development is still unclear. Even though fusing gametes are presumed to be epigenetically reprogramed during fertilization with erasure of all epigenetic tags, about 1% of these tags are imprinted and retained across generations.[134,135] Maternal epigenetic information in the oocyte could also directly influence the primordial germ cells.[136,137]

In a fetus or young infant, some HSCs in the bone marrow differentiate into monocytes and macrophages.[1,138] These monocytes are released into the peripheral blood, where these cells circulate for up to 5 days[3,139] and then enter various tissues other than the CNS, to differentiate into macrophages.[140] The PRRs in these HSCs get epigenetically programed and display altered responses to infections. The innate inflammatory pathways seem generally suppressed in the HSCs, but a large repertoire of metabolic enzymes is active.[21,140,141] Most of this genetic imprinting occurs within the first 24 hours.[142] In infants with bacterial infections, the MDMs) may display IIM traits for a few weeks.[23,27,125,131] In comparison, adult macrophages get primed sooner and show specific memory traits for longer periods.[27,143] However, these changes may be altered by infections or vaccination in all age groups.[3]

Macrophages have traditionally been perceived as relatively plastic cells.[144] However, recent data combining fate-mapping, single-cell transcriptomics, and epigenetics show that prolonged residence in tissue-specific niches can rewire or override their transcriptional program in the local microenvironment.[145] These cells likely also get imprinted from the conditions at the time of recruitment.[35,146] The accessibility of the promoters/enhancers in the cellular DNA to transcription factors and RNA polymerases can result in chromatin remodeling.[147,148] The remodeling may include DNA compaction, DNA methylation, histone modifications (methylation, acetylation, phosphorylation, and citrullination), and gene priming by regulators such as the upstream master long non-coding ribonucleic acid (lncRNA) of the inflammatory chemokine locus (UMILILO).[35,149–152]

Histone Modifications

Epigenetic modifications of histones plays an important role in IIM in macrophages.[123,153,154] Histone modifications can affect histone–histone and histone–DNA interactions, binding to chaperones, and chromatin structure (Fig. 6).[155,156] The most dynamic histone epigenomic mark is histone acetylation in the nucleosomes.[157] This mark is frequently located close to gene promoters and enhancers, and therefore correlates well with changes in gene expression. Histone methylation in actively expressed gene promoters can affect both the levels and the plasticity of transcription.[149,157]

The effects of histone acetylation on the promoters and enhancers of inflammatory genes have evoked considerable interest; H3K27ac seems to be a key determinant of the expression of immune response factors;[123] it is often seen in the enhancers and promoters of many genes that are typically inactive.[158–160] H3K9ac and H3K56ac are involved in nucleosome–DNA interactions and are rapidly and reversibly reduced in response to DNA damage.[161,162] H4K91ac leads to nucleosome instability.[163] Many histone modifications can be identified even after the primary stimulus is no longer active, and can facilitate the transcription of inflammatory genes upon restimulation.[164] Some of the so-called "latent" enhancers are not pre-marked in naïve cells but acquire histone modifications upon primary stimulation.[123,165] After the removal of the stimulus, some of these latent enhancers still retain the histone modifications and show rapid, stronger activation upon restimulation.

The effects of histone methylation are also important. These vary with the particular types of histones that are methylated, the number of methyl groups added, and the presence of acetylation in nearby regions.[149] For instance, trimethylation of lysine 4 in histone 3 (H3K4me3) and H3K4me1 can activate promoters and enhancers, respectively.[166,167] In unstimulated macrophages, chromatin regions containing inflammatory genes are compacted and largely not accessible for transcription. Primary stimulation with the antigens/pathogens recruits various transcription factors, such as activator protein 1 AP-1; the signal transducers and activators of transcription STATs; and nuclear factor-kappa B (NF-kB) to the promoters and enhancers, which are already pre-marked in the naïve cells by the lineage-specific PU.1 transcription factor.[168–171] When challenged again with the same or a different antigen/pathogen, the chromatin shows increased decondensation, demethylation of DNA, and modifications of histone 3 (H3) such as tri-methylation of lysine 4 (K4; H3K4me3), mono-methylation (H3K4me1), and acetylation of lysine 27 (H3K27ac).[172,173] These epigenetic changes lead to enhanced transcription and translation of immune response factors (Fig. 7).[174]

H3K27 methylation has been associated with both gene activation and repression.[175–177] Many models show concomitant methylation and acetylation, and the effects have not been easy to predict.[123,155] The silencing effects of histone methylation might not always be independent and could involve additional regulators such as the polycomb group proteins.[27,177–181] Trained macrophages show H3K4me1 and H3K27ac in the enhancers and promoters of many genes that are typically inactive.[158–160]

Bacillus Calmette-Guérin inoculation increases resistance to *Staphylococcus aureus* by upregulating H3K4me3 levels associated with inflammatory genes IL-1β and TNF.[120,182] In contrast, β-glucan training increased H3K4me3 and H3K27ac in at least 500 gene promoters.[154,183] Upon secondary stimulation, these leukocytes showed increased expression of transcription factors, cytokines, and phenotypic/functional changes seen in acute inflammation.[23,183] The temporal stability of various changes is also variable. H3K4me1 persisted for long periods but H3K27ac was eliminated sooner after the stimulus was removed.[184,185]

Age, both of the cells and of the host, is an important determinant of the effects of LPS on IIM macrophages.[186] The intensity of immune responses is higher in the developing fetus and neonate.[1,9,14,15,112–114,187–189] Ageing in macrophages impacts many processes including TLR signaling, polarization, phagocytosis, and wound repair.[190–192] Even though the innate immune system is in a "quiescent" mode at birth,[193,194] the mucosal surfaces in the lung and the gastrointestinal tract contain a large number of macrophages. Most of these cells show low baseline expression of MHC-II, F4/80, CD68, CD80, and CD86[193,194]; these low levels of expression may be teleologically important to minimize inflammation when exposed to various environmental and physical challenges soon after birth.[193,195] However, these cells express an M1-like phenotype which can get quickly primed and display highly enhanced immune responses with proinflammatory cytokines, iNOS, and CD86 following LPS stimulation at much higher levels than in adults.[186,193] Arginase-1, which plays anti-inflammatory roles, is also decreased.[193] These characteristics are consistent with the high protein levels of the inducible nuclear factor NF-κB and the pro-inflammatory characteristics seen in neonatal macrophages.[171,193]

The number of macrophages in various mucosal organs in neonates also differs from that in adults in various organs.[115,193] Even though LPS is recognized as the primary pathogen-associated molecule that triggers host innate immune responses to bacterial invasion, the phenotypical modulation of macrophages in response to the various components of the microbiome may vary.[115] M1 is the predominant mucosal macrophage subtype in most such responses.[115,193]

Compared to naïve macrophages, differentiation of these cells leads to a baseline increase in the expression of inflammatory cytokines such as TNF and IL-6. An initial exposure to low doses of LPS primes neonatal macrophages, and a later secondary application further stimulates the expression of inflammatory mediators. Such induction of these mediators is not seen in adult macrophages. In contrast, the application of LPS in high doses suppresses the inflammatory responses in both neonatal and adult macrophages (Fig. 5).[122,155,196] These changes have been associated with increased H3K9me2 and H3K27me2, which downregulated TNF and other inflammatory cytokines.[155,197–199] Lipopolysaccharide-induced tolerance was marked by increased phosphorylation of the transcription factor cyclic associated molecular pattern (AMP)-dependent transcription factor 7 (ATF7).[200,201] H3K9me2 levels were decreased.[200–202]

In newly recruited monocytes in various tissues, there may be up to 8,000 epigenetically dynamic regions where histone acetylation is the most prominent change.[3,154] Histone methylation H3K4me1 is increased in distal regulatory regions, which are relatively stable and might represent decommissioned regulatory elements.[141] β-glucan priming can induce up to 3,000 distal regulatory elements, whereas LPS-tolerization may induce H3K27ac at 500 distal regulatory regions.[3,141] Gene modules that mediate LPS tolerance are more active in monocytes than in naïve macrophages.[3,155] About 12% of known human transcription factors displayed variation in expression during macrophage differentiation, training, and tolerance.[3]

Several other mechanisms are also being studied. Cytokines such as IL-12 may play an important role.[35] A reverse adaptive-to-innate directionality of memory formation is another possibility, as noted in a respiratory adenoviral infection model.[125] In lungs, memory AMs can develop and sustain independently of blood monocytes. The CD8-T cells, which are known adaptive effectors, can help prime, but not maintain, memory AMs by producing IFN-γ. Memory macrophages can also help maintain antibacterial immunity by stimulating the neutrophil populations.[203]

Effects of MicroRNAs

MicroRNAs (miRNAs) can promote prolonged epigenetic changes and LPS tolerance in IIM macrophages.[204,205] High miR-155 levels were associated with inflammatory activation.[206,207] Prolonged exposure to LPS increased miR-221 and miR-222 levels.[208,209] These miRNAs silenced the inflammatory genes through switch/sucrose non-fermentable (SWI/SNF) and signal transducer and activator of transcription (STAT)-mediated chromatin remodeling.[210–212]

As currently understood, miRNAs silence gene expression by repressing cap-dependent translation.[213] These also destabilize the target mRNAs through deadenylation, decapping, and then degradation from the 5´ to the 3´ ends.[214] The miRNA-induced silencing complexes (miRISCs) involve interactions of the conserved GW182 proteins (named after the glycine and tryptophan repeats and the molecular weight) with the argonaute proteins (discovered in *Arabidopsis thaliana*) and downstream deadenylases.[215] These protein–protein interactions, in turn, increase (a) biogenesis of small RNAs[216]; (b) insertion of tryptophan residues into hydrophobic pockets on the surface of argonaute proteins[217]; (c) displacement of the translation initiation factors 4A[218]; and/or (d) recruitment of the translational repressor and decapping of the activator DEAD box protein 6.[219]

Effects of Metabolic Changes

Classically activated M1 macrophages produce energy largely through glycolysis, whereas M2 macrophages utilize oxidative phosphorylation and the tricarboxylic acid cycle (TCA; citric acid cycle).[220,221] Treatment with β-glucan or BCG augment aerobic glycolysis via the Akt/mechanistic target of rapamycin (mTOR)/hypoxia-inducible factor-1α (HIF-1α) pathway.[222,223] In M1 macrophages, oxidative phosphorylation begins after the acute phase response ends.[224,225]

Cellular metabolism in macrophages is closely related to epigenetic changes.[150,226] The epigenetic profile of histones is closely related to the activity of two sets of enzymes, the histone acetyltransferases (HATs) and the histone deacetylases (HDACs).[227,228] These induce posttranslational modifications on histones, which in turn, can alter chromatin structure and function.[229,230] HATs acetylate the *N*-terminal histone tail to induce a “relaxed” chromatin structure that allows transcriptional activation.[227,231] In contrast, HDACs repress transcription by tightening the chromatin structure and rendering the associated DNA less accessible for transcription.[232,233]

Histone deacetylases 1 and 6 promote the development of the immune phenotype of macrophages.[234–236] Trained monocytes typically show high levels of histone acetylation, which correlates with the acetyl-coenzyme A (acetyl-CoA) levels.[65,154] Tricarboxylic acid cycle intermediates such as fumarate, succinic acid, and α-ketoglutaric acid (α-KG) can also promote IIM.[66,237] These cells typically show low demethylase activity but high levels of cholesterol synthesis, which promote epigenetic reprogramming by activating the mTOR pathway.[25,154,238] Glutamine metabolism is also associated with increased succinic acid and α-KG, which activate epigenetic enzymes to enhance M2-related H3K27me3, which in turn, suppresses these genes and turns memory macrophages into an anti-inflammatory phenotype.[66,123,224] In cells with LPS-induced endotoxin tolerance, α-KG promotes M1 activation of macrophages.[224,239] These results suggest that cellular metabolism can alter immune memory.

Role of IIM Macrophage in Diseases in Adult Patients/Animal Models

Innate immune memory in macrophages can alter the responses to many pathogenic stimuli.[23,240] Most work has been done in diseases of adulthood, but these data could provide useful insights into the susceptibility and pathogenesis of many neonatal conditions.[241–243]

Acute Inflammation—Inflammatory macrophages can both express and promote the expression of TNF, IL-1β, and IL-8 in neighboring cells.[10] Interestingly, mice treated with IL-1β prior to a second bacterial infection showed increased IIM macrophages and improved survival.[244] In this model, IIM macrophages express higher H3K4me3 levels (unpublished data from our laboratory). β-glucan is another inducer of IIM macrophages; it can reprogram macrophages by curtailing the activation of inflammasomes containing the NOD-like receptor family pyrin domain-containing-3 (NLRP3).[245,246] NLRP3 can detect markers of cellular damage such as extracellular ATP and crystalline uric acid.[4,247]

Infectious Diseases—Macrophages provide innate immunity against bacterial and viral infections, and IIM macrophages can enhance the defenses against *S. aureus* skin infections.[4,28,248] In murine models, these macrophages showed increased monocyte recruitment, bacterial killing, healing, and resistance to secondary infections.[248,249] In the lungs, AMs can be activated by a primary respiratory syncytial virus infection with improved host defense against pneumococcal superinfections.[250] Memory AMs express major histocompatibility complex (MHC)-II and chemokines at higher levels, and show more glycolysis and bacterial killing.[4,203,249–251]

Infection-induced IIM has been associated with molecules such as NOD2; possibly viral RNA; and proteins containing a leucine-rich repeats (*LRR*)-containing domain are evolutionarily conserved in many *proteins* associated with innate immunity.[252] Similarly, *NLRP3* (NOD-, LRR- and pyrin domain-containing protein 3), which is an intracellular sensor that detects many microbial molecules may also be associated.[253,254] The BCG vaccine can activate NOD2-dependent pathways to protect against secondary infections through epigenetic reprogramming of monocytes/macrophages.[121,255] In the resulting memory macrophages, the promoters of IL-6 and TNF genes can increase H3 trimethylation (H3K4me3) and induce the expression of these cytokines.[121,256]

Allergic Disorders—Infectious agents can induce IIM in macrophages, but similar changes are frequently seen in allergic and other type 2 inflammatory conditions.[257] M2-polarized macrophages may play a role in asthma[258]; AMs in these patients express chemoattractants such as CCL17,[259–261] and eicosanoids, particularly leukotrienes, which can stimulate T helper-2 cells.[262,263] Pathogen molecules, sterile inflammatory stimuli, and respiratory viruses can induce epigenetic and metabolic reprogramming in macrophages, and thereby alter responsiveness and effector functions similar to those seen in allergic disorders.[257] These IIM changes can be seen both in tissue macrophages and myeloid progenitors.[4,257,264,265] Evaluation of epigenetic/histone-profiles such as *H3K27me3* and H3K9me3 may help develop focused therapies.[4,266]

Transplant Rejection—Innate immune memory macrophages may increase the risk of transplant rejection by activating innate and adaptive immunological responses and consequent inflammation.[267,268] Macrophages may recognize MHC-I molecules and generate memory.[269] In murine kidney and heart transplantation, deletion of recipient [type A paired immunoglobulin-like receptors (PIR-A)] or blocking the binding of PIR-A to donor MHC-I molecules can block the memory response and alleviate the rejection reaction.[270,271] Such IIM has also been seen in human transplant cases.[27] Macrophages can acquire IIM for recognizing alloantigens, and blocking this memory may improve the outcomes of transplantation.[272,273]

Atherosclerosis—Innate immune memory macrophages can protect against atherosclerosis.[274] In addition to the classical inducers of innate immunity such as β-glucan, BCG, and LPS, endogenous non-microbial atherogenic stimuli such as high cholesterol levels, oxidized low-density lipoprotein (oxLDL), and lipoprotein(a) can also promote IIM in macrophages.[275]

Oxidized low-density lipoprotein is a recognized DAMP; it can increase macrophage recruitment, inflammation, and interstitial fibrosis.[276,277] It recruits macrophages binds the CD36 receptor to, increases glycolysis, increases the production of pro-inflammatory factors, and induces IIM.[278] Upon stimulation by TLR2 and TLR4 ligands, oxLDL-stimulated macrophages produce inflammatory factors such as TNF, IL-6, and collagenases such as matrix metalloproteinase (MMP)-2 and -9. These mediators can destabilize atherosclerosis plaques.[279] Tumor necrosis factor promoters are enriched in H3K4me3 markers.[280]

Neoplasms—Innate immune memory macrophages have been detected in several tumors.[281,282] These findings might not be clinically relevant in neonates but may still provide important mechanistic insights. Inflammatory M1 macrophages can provide anti-tumor immunity; β-glucan can induce type I IFN signaling, and BCG can be useful for directly stimulating macrophages.[4,65,120,283,284] Innate immune memory macrophages with M1-like properties can promote tumor progression with angiogenesis, fibrosis, and consequent tissue remodeling.[65,140] These macrophages show histone modifications such as H3K4me3 and H3K9me3, and upregulated expression of inflammatory and other genes associated with tumor progression.[285]

Conclusions

With adaptive immune responses still maturing, macrophages are a much-needed component of immune responses in the fetus and the newborn infant.[1,9,112–114] Innate immune memory macrophages may be crucial for trained/acquired host immunity in the fetus/young infant, but we still have major gaps in our understanding of the functional maturation of these cells.[1] These details will be of translational importance for developing therapeutic interventions in various inflammatory diseases.

Single-cell transcriptomics and epigenomics have helped identify IIM macrophage precursors.[286] Studies of tumor-associated macrophages may also be useful; understanding the developmental regression with persistent activation of these macrophages can provide useful clues into the ontogeny of macrophage subpopulations, macrophage memory, and the involved molecular mechanisms.[287,288] These findings can then be evaluated in appropriate fetal and genetically altered animal models.[123,289–298]

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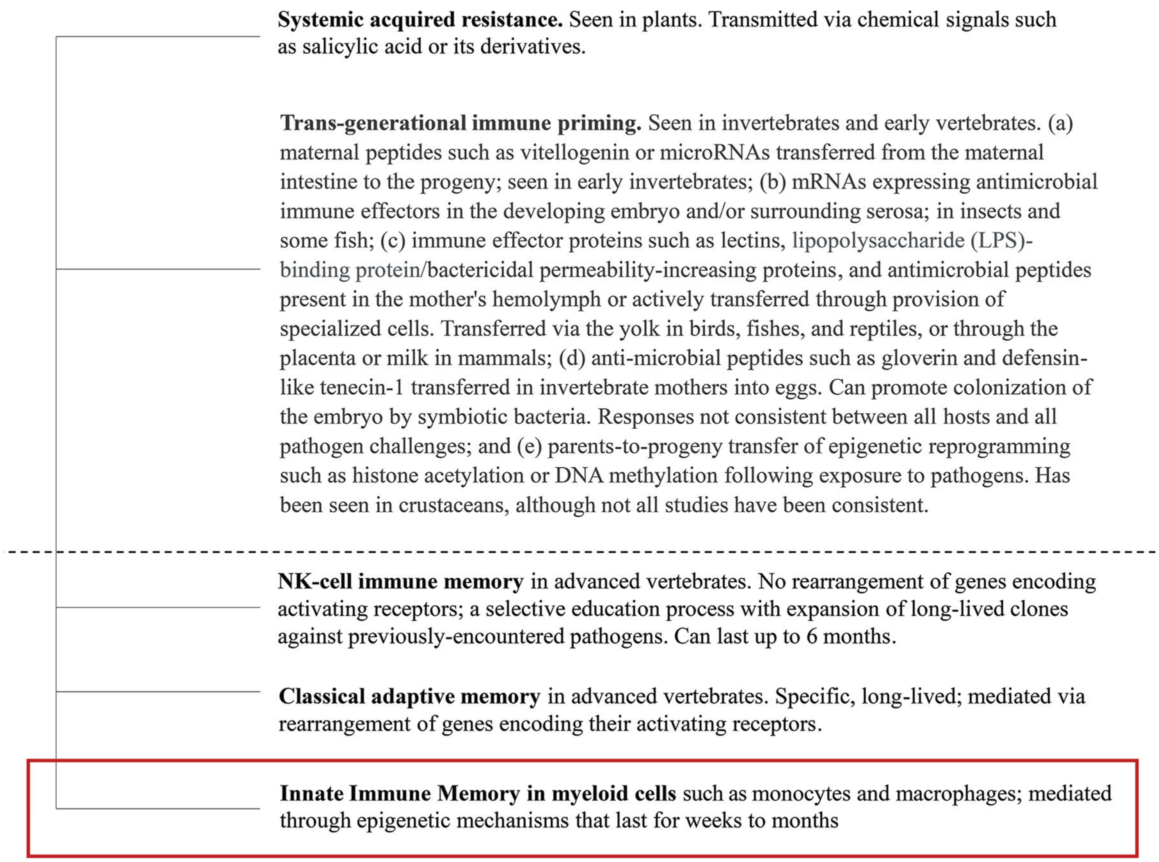
Key Points

- Macrophages have so far been recognized as the primary mediators of innate immunity. However, emerging information suggests that macrophage responses may be altered, either enhanced or suppressed, based on earlier infectious or other immunological stimulation.
- The memory of prior stimulation in macrophages is less accurate in terms of antigen specificity, but is analogous to that seen in adaptive immune responses. It has been described as “trained immunity” or the “innate immune memory (IIM)”.
- The likely mechanism(s) of IIM in macrophages are rooted in epigenetic reprogramming and metabolic alterations.
- Understanding macrophage IIM may be particularly important in the context of the maturing fetus/neonates who are yet to develop protective levels of adaptive immunity.



Systemic acquired resistance. Seen in plants. Transmitted via chemical signals such as salicylic acid or its derivatives.

Trans-generational immune priming. Seen in invertebrates and early vertebrates. (a) maternal peptides such as vitellogenin or microRNAs transferred from the maternal intestine to the progeny; seen in early invertebrates; (b) mRNAs expressing antimicrobial immune effectors in the developing embryo and/or surrounding serosa; in insects and some fish; (c) immune effector proteins such as lectins, lipopolysaccharide (LPS)-binding protein/bactericidal permeability-increasing proteins, and antimicrobial peptides present in the mother's hemolymph or actively transferred through provision of specialized cells. Transferred via the yolk in birds, fishes, and reptiles, or through the placenta or milk in mammals; (d) anti-microbial peptides such as gloverin and defensin-like tenecin-1 transferred in invertebrate mothers into eggs. Can promote colonization of the embryo by symbiotic bacteria. Responses not consistent between all hosts and all pathogen challenges; and (e) parents-to-progeny transfer of epigenetic reprogramming such as histone acetylation or DNA methylation following exposure to pathogens. Has been seen in crustaceans, although not all studies have been consistent.

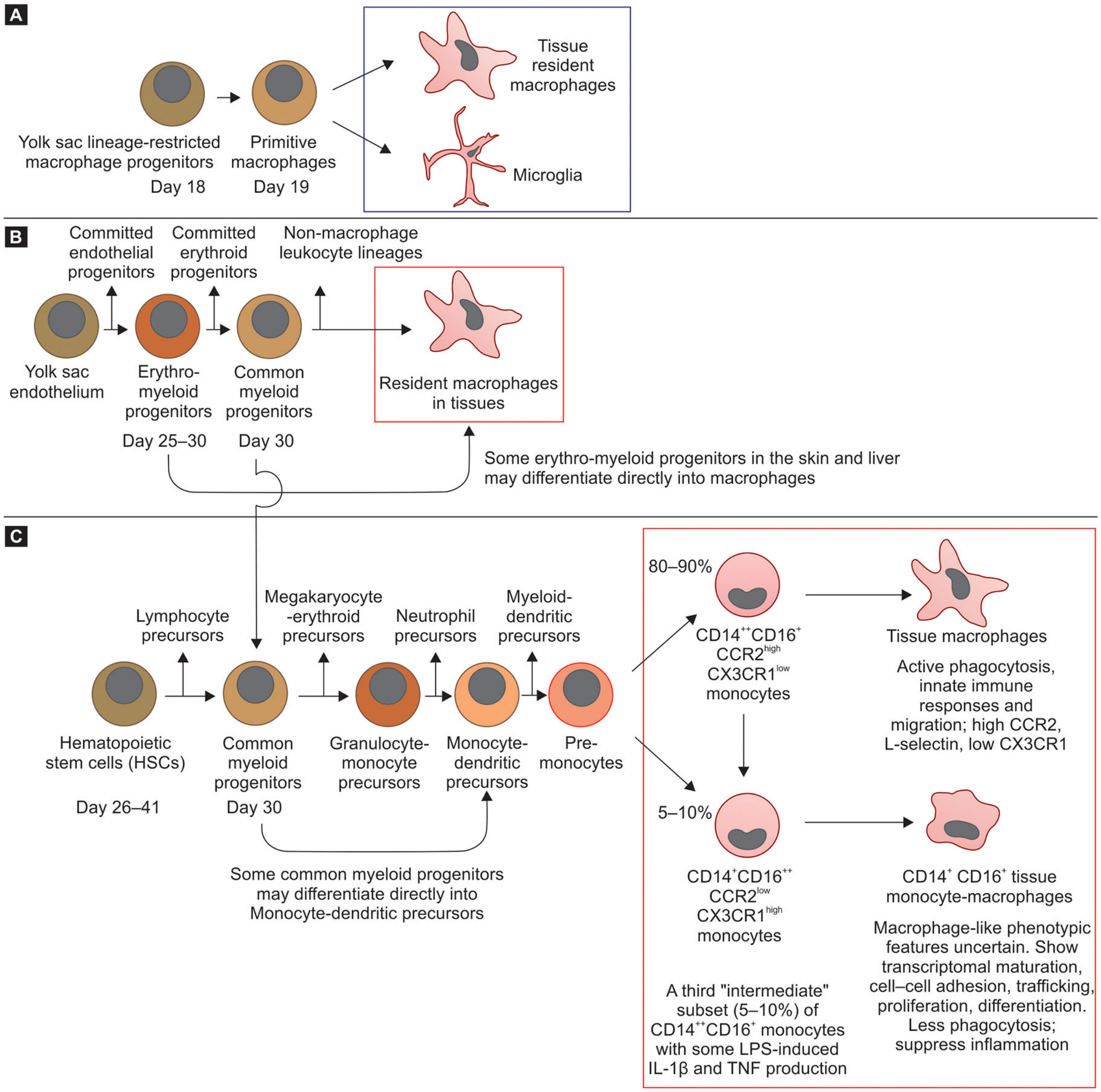
NK-cell immune memory in advanced vertebrates. No rearrangement of genes encoding activating receptors; a selective education process with expansion of long-lived clones against previously-encountered pathogens. Can last up to 6 months.

Classical adaptive memory in advanced vertebrates. Specific, long-lived; mediated via rearrangement of genes encoding their activating receptors.

Innate Immune Memory in myeloid cells such as monocytes and macrophages; mediated through epigenetic mechanisms that last for weeks to months

Fig. 1:

Phylogenetic evolution of immune memory. Five categories of immune memory have been recognized: (1) Systemic acquired resistance, as seen in plants; (2) Transgenerational immune priming, which may include vertical transmission of immune experience from parents to the offspring; horizontal transfer between individuals, and between individuals and other parents' offspring; (3) NK-cell immune memory; (4) Classical adaptive memory, as seen in vertebrates; and (5) IIM in myeloid cells. The broken line separates NK-cell immune memory, classic adaptive memory, and the IIM myeloid cells as these are seen in evolutionarily advanced vertebrates. The IIM myeloid cells are the focus of the current article and have been highlighted in a red-outlined box



Figs 2A to C:

Macrophage differentiation. Schematic shows macrophage development from lineage-restricted embryonic progenitors. The terminally differentiated embryonic and hepatic macrophages, and bone marrow-derived monocytes and macrophages are highlighted in rectangular borders as these are the stages of differentiation where some cells get committed for innate immune memory. (A) lineage-restricted embryonic progenitors; (B) YS endothelium, which differentiates into EMP and then into CMPs. Some CMPs differentiate into macrophages and other primitive leukocytes, whereas others differentiate into GMPs and then in sequential steps into macrophages as shown in panel C; (C) HSC in sequential stages of CMPs GMPs, monocyte-dendritic precursors, pre-monocytes, M1 or M2 (and possibly an intermediate subtype) monocytes and then into corresponding macrophages. The stages at which IIM appears have been highlighted by enclosing those in rectangular borders

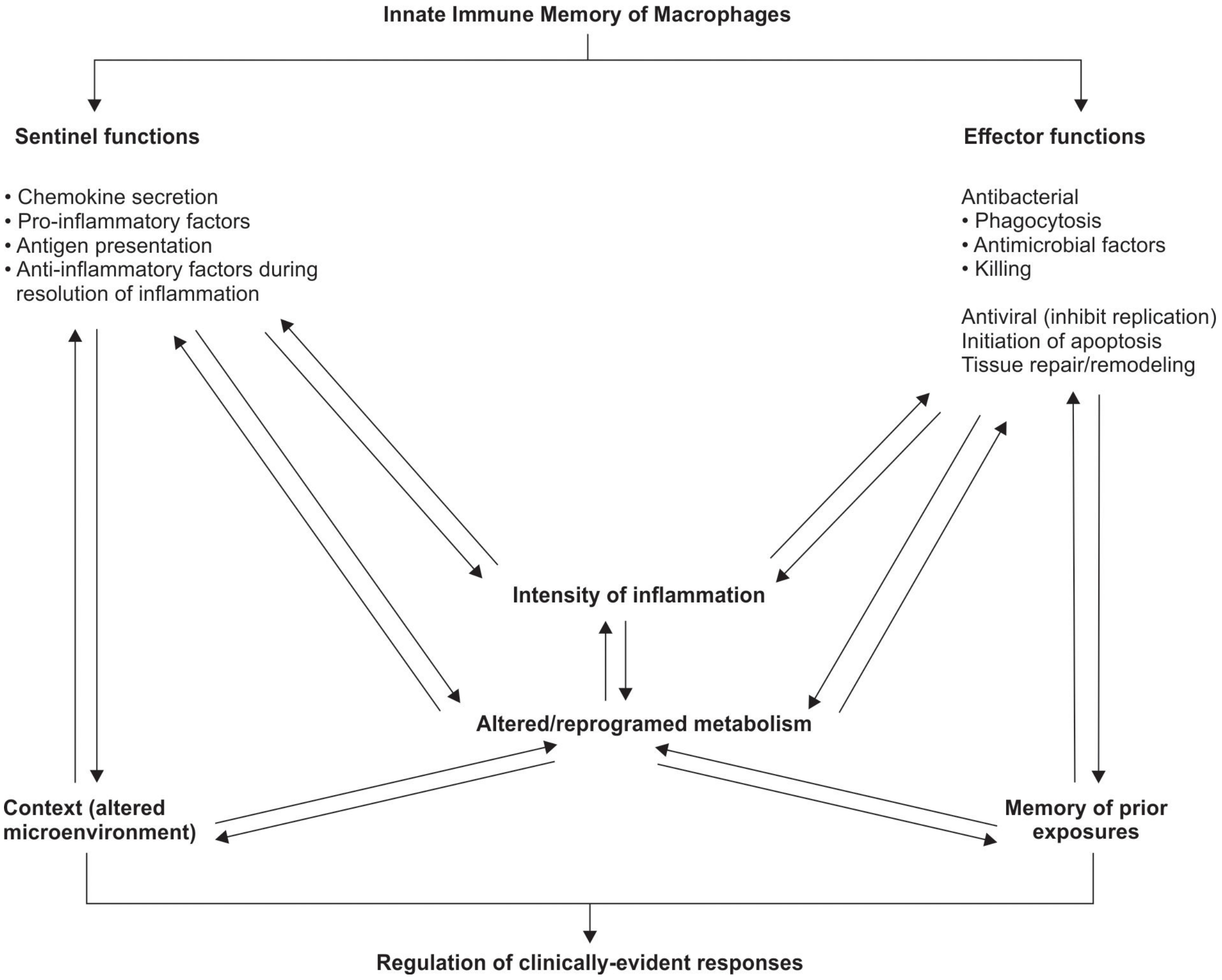


Fig. 3:

Innate immune memory of macrophages affects both the sentinel and effector functions of these leukocytes. The context (altered microenvironment) and memory of prior exposures are important variables in the regulation of clinically evident responses

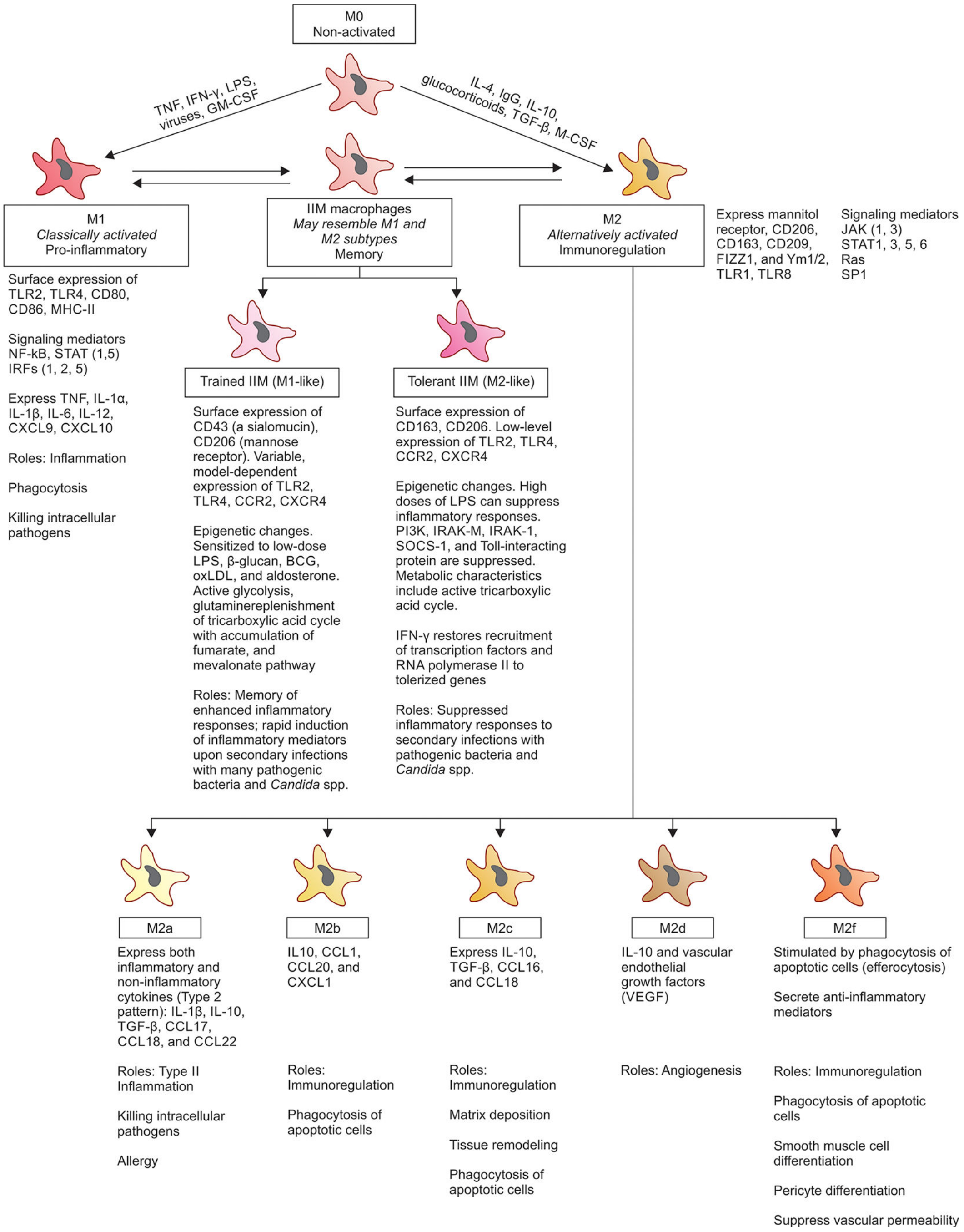


Fig. 4:

Differentiation of MDMs. Schematic shows differentiation of naïve macrophages into classically activated M1, the IIM macrophages, and the alternatively activated M2 subclasses. The surface markers and key signaling mediators are depicted with each group. The IIM macrophages, including the trained (M1-like) and the tolerant (M2-like) subgroups, do not match the other categories and may need to be classified separately. The M2 macrophages may be comprised of 5 subgroups with distinct inflammatory functions and physiological roles

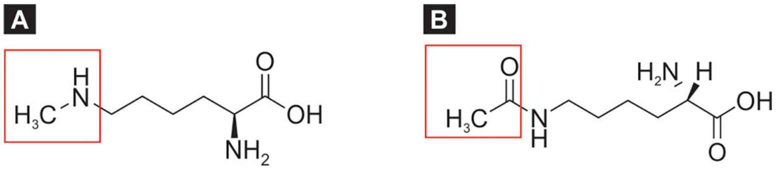


Fig. 5:

Schematic figure showing (A) methylated (CH_3) lysine (K). On histone 3, lysine (K) residues on positions 4 (H3K4) and 27 (H3K27) can be mono- [(6-*N*)-methyl lysine], di- [(6-*N*,6-*N*) dimethyl lysine], or trimethylated [(6-*N*,6-*N*,6-*N*) trimethyl lysine]. These H3K4 sites are usually located close to the transcription start sites or enhancers of various genes; (B) acetyl [$C(O)CH_3$) lysine (or acetylated lysine) is an acetyl-derivative of the amino acid lysine. These residues are important in epigenetics as regulators of binding of histones to DNA in nucleosomes and thereby controlling the expression of genes on that segment of DNA

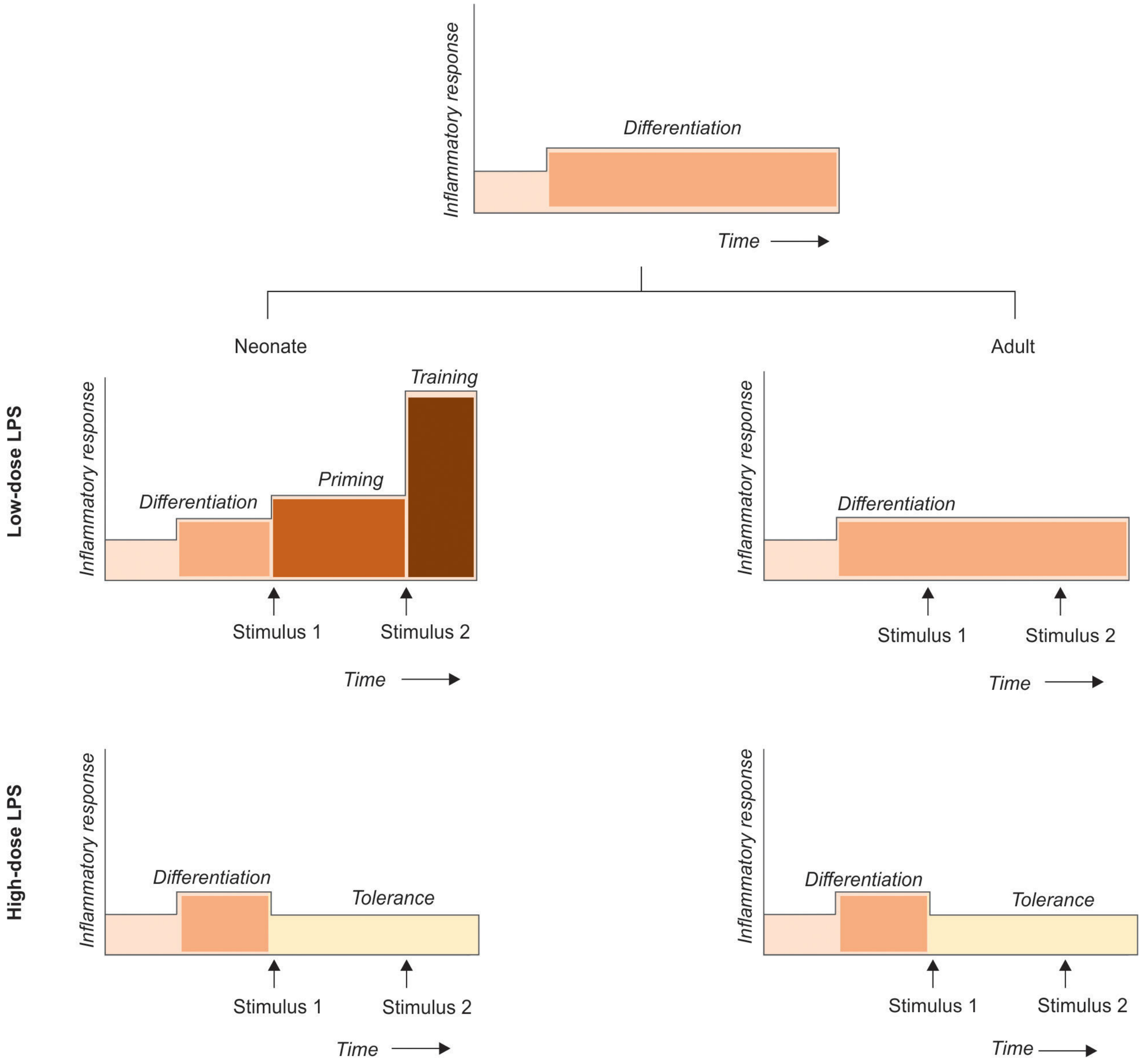
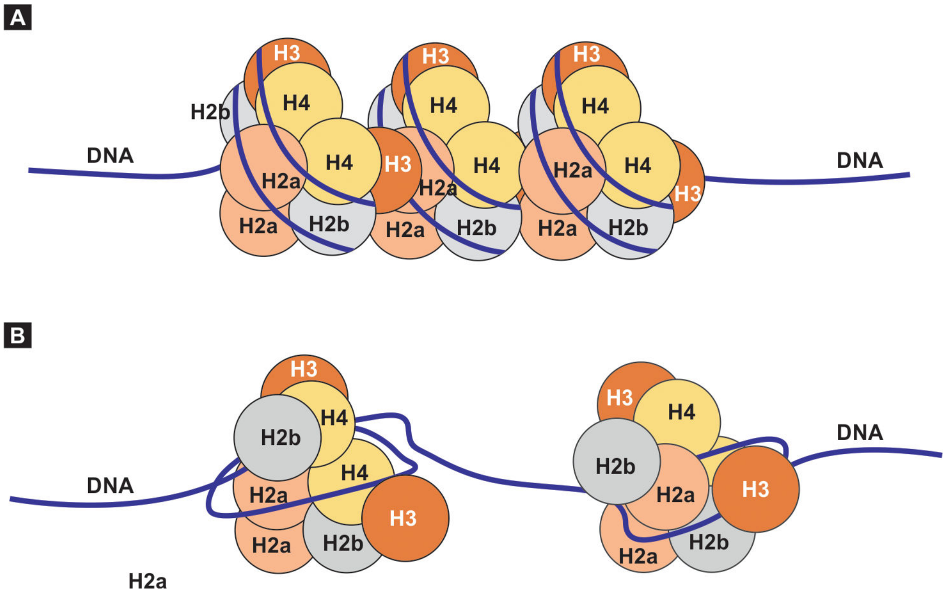


Fig. 6:

Effect of age on the effects of LPS on macrophage IIM. Differentiation of naïve macrophages leads to a baseline increase in the expression of inflammatory cytokines such as TNF and/or IL-6. Subsequently, an initial application of LPS in low-doses primes neonatal macrophages for expression of inflammatory mediators. Re-application of LPS in these same doses trains the macrophages and can induce a hyper-inflammatory response. Such induction of these mediators is not seen in mature macrophages in adults. Application of LPS in higher doses suppresses the inflammatory responses in both neonatal and adult macrophages



Figs 7A and B:

Chromatin condensation state affects gene expression. (A) Chromatin housing the immune response genes in naïve (unstimulated) macrophages is highly condensed (heterochromatin state) due to high methylation of DNA, making these genes inaccessible to the transcription factors. These genes are completely silenced or transcribed at very low levels. (B) Stimulation with a pathogen/danger signals demethylates DNA, decondenses chromatin (euchromatin state), and makes these genes accessible for transcription

Table 1:

Macrophage subpopulations

Macrophage subpopulation	Activation	Function	Biological processes
MO	Naïve, unstimulated macrophages		
M1	Inflammatory macrophages		
	- LPS and interferon-γ. - macrophage-produced inducible nitric oxide synthase.[299] - macrophage-produced IL-12, IL-18, and IL-23.[300]	- pro-inflammatory, antimicrobial. - regulate angiogenesis.[299,301,302] - matrix composition; express MMP-1, MMP-3, and MMP-10.[303]	- activate Tie-signaling.[304] - promote endothelial cell chemotaxis, and migration of other cells involved in angiogenesis.[305]
IIM	Innate immune memory macrophages		
Trained (Ml-like)	- low-dose LPS, β-glucan, BCG, oxLDL, and aldosterone-trained macrophages.[155]	memory of previous infections, which can rapidly recruit and activate innate immune cells.[30] - rapid induction of inflammatory mediators upon secondary infections with pathogenic bacteria and *Candida* spp.[306]	- host defense. Particularly important in neonates and young infants before adaptive immunity becomes functionally adequate.[307]
Tolerized (M2-like)	- epigenetic changes involved in development. High doses of LPS can suppress inflammatory responses.[155]	- memory of previous infections; can suppress unduly severe inflammatory responses.[23]	- host protection. May protect young infants, who are still developing adaptive responses, from severe tissue damage.[23]
M2	Anti-inflammatory, pro-healing macrophages		
M2a	Cytokines, IL-4, IL-13.[308]	- regulate the expression of platelet-derived growth factor-BB and transforming growth factor-β.[299]	- support pericyte and smooth muscle cell differentiation.[304]
M2b	- immune complexes, IL-1β and molecules with PAMs.[309] - immune complexes and TLR ligands.[310]	- express inflammatory cytokines (IL-1, IL-6, and TNF), and antiinflammatory IL-10.[10]	- altered regulation of the PI3K/Akt/FoxO3a pathway.[311]
M2c	- IL-10, TGF-β, and glucocorticoids.[312]	- express MMPs.[312] - express IL-10, TGF-β, and pentraxin-3.[313]	- vascular remodeling.[299]
M2d	- TLR agonists.[224] - adenosine A2A receptor agonists.[314]	- suppress inflammatory responses.[115]	- regulate the expression of IL-10 and VEGF.[315]
M2f	- phagocytosis of apoptotic cells.[316] - upregulate TGF-β_1.[304]	- express anti-inflammatory mediators.[304]	- regulate vascular permeability.[304]

Table 2:

Innate and adaptive immune memory

	IIM in macrophages	Cells with intermediate properties	Adaptive immune memory
Cells	IIM in monocytes/macrophages	Seen in B1 and marginal zone B-cells; invariant natural killer (iNKT)-cells; innate lymphoid cells, and γδ T-cells	Seen in circulating αβ T- and B-lymphocytes; CD8αα-expressing intestinal intraepithelial lymphocytes
Phylogeny	Plants, invertebrates, early vertebrates	Vertebrates	Higher vertebrates
Mechanism	Epigenetic reprogramming, cell metabolic change	Genetic programming and restrictions; produce IgM. Invariant NKT cells interact with a few lipid antigens; γδ T-cells recognize antigens without the major histocompatibility complex	Genetic programming; antigen-specific immunity through gene rearrangement. Produce immunoglobulins, particularly IgG and IgD
Human age groups	All	B1 cells in fetal-neonatal period. Other cells seen in all ages	All
Duration	Weeks to months	Weeks to months	Weeks to months
Specificity	No	Limited; initiate and amplify both innate and adaptive immune responses	Yes

Table 3:

Signaling programs in macrophage “training”

Stimulant	Receptor	Training immunity signaling	Metabolic remodeling	Epigenetic remodeling
β-glucan	Dectin-1	Akt-mTOR-HIF-1α IL-1, GM-CSF/CD131	Glycolysis	H3K4me1[129]
			Glutaminolysis	H3K4me3[317]
			Mevalonate synthesis	H3K27ac[318]
BCG	NOD2	Akt-mTOR, IFN-γ, IL-32	Glycolysis	H3K9me3[319]
			Glutaminolysis	H3K4me3[319]
			Mevalonate synthesis	H3K27ac[320]
OxLDL	TLRs, oxLDL receptor	mTOR-dependent ROS	Glycolysis, mevalonate synthesis	H3K4me3[275]
LPS	TLR4	IRAK-M, Tollip, JNK-miR24, ATF7	Glucose and cholesterol metabolism	H3K4me1, H3K4me3, H3K9me2, H2K27me[24]
Aldosterone	Mineralocorticoid	Fatty acid synthesis pathway	Fatty acid synthesis	H3K4me3[321]
HMGB1	TLR RAGE	IRAK-M		Inhibits methylation of H3K9 and other histones.[322] C-terminal tail of HMGB1 interacts with the core histones, including H3 and H2A-H2B dimers to stimulate transcription[323]
Fungal chitin	Several possible receptors, including TLR2, TLR3, TLR8, TLR9, FIBCD1, LYSMD3, NOD2, mannose receptor	Binds TLR2 Endosomal ligands of TLR3 (ligand Poly I:C), TLR8 (risiqui- mod), TLR9 (CpG)		Histone methylation.[154] Limited details so far
Uric acid	Clec12a (negative receptor)	IL-1β, Akt		Histone methylation.[324] Limited details so far

Akt, Ak strain transforming serine/threonine-protein kinase (“Ak” in Akt refers to the AKR mouse strain that develops spontaneous thymic lymphomas, “t” stands for “thymoma”); GM-CSF, granulocyte macrophage-colony stimulating factor; H3K14ac, histone 3 lysine 14 acetylation; H3K27ac, histone 3 lysine 27 acetylation; H3K4m3, histone 3 lysine 4 trimethylation; H3K9m2, histone 3 lysine 9 dimethylation; H3K9me2, histone 3 lysine 9 dimethylation; HIF-1α, hypoxia-inducible factor 1α; HMGB1, high mobility group box 1; IFN-γ, interferon γ; IRAK-M, IL-1 receptor-associated kinase M; LPS, lipopolysaccharides; mTOR, mammalian target of rapamycin; NOD2, nucleotide-binding oligomerization domain-containing protein 2; Tollip, toll-interacting protein; oxLDL, oxidized low-density lipoprotein; PLZF, promyelocytic leukemia zinc finger; RAGE, receptor for advanced glycation end-products; ROS, reactive oxygen species; TLR, toll-like receptor; FIBCD1, fibrinogen C containing domain 1 (FIBCD1); LYSMD3, LysM domain containing 3; Clec12a, C-type lectin domain family 12 member A; CpG, cytosine and guanine nucleotides with the “p” representing the linking phosphate