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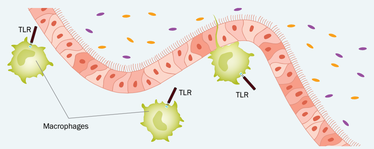
The Complex Biology of Macrophages: Origins, Functions, & Activation States

Common Macrophage Markers

B7-1/CD80
B7-2/CD86
CCR5
CD11b/Integrin αM
CD11c
CD14
CD15 (SSEA-1)/Lewis X
CD68/SR-D1
CD163
EMR1 (Human)
F4/80 (Mouse)
Fcγ RI/CD64
Fcγ RII/CD32
Fcγ RIII/CD16
Galectin-3/Mac-2
GITR Ligand
HLA-DR
Integrin αL/CD11a
LAMP2/CD107b
LILRB4/CD85k/ILT3
M-CSF R/CD115
MHC Class II
Siglec-3/CD33
TLR2
TLR4

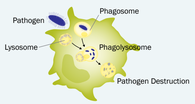
Common Macrophage Functions

Immune Surveillance

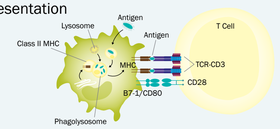


Phagocytosis

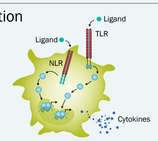
Removal of:
- Dead/Dying cells/Debris
- Pathogens
- Toxins



Antigen Presentation



Cytokine Production

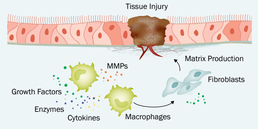


Wound Healing and Tissue Remodeling

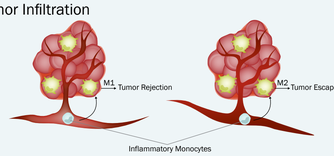
Inflammatory:
- Phagocytosis
- Antigen Presentation
- Pro-inflammatory Cytokine Production

Proliferative:
- Fibroblast Recruitment/Activation
- ECM Formation
- Reepithelialization
- Neovascularization/Angiogenesis

Remodeling:
- ECM Composition Modifications
- ECM Protein Synthesis

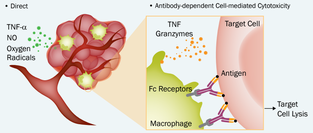


Tumor Infiltration



Cytotoxicity

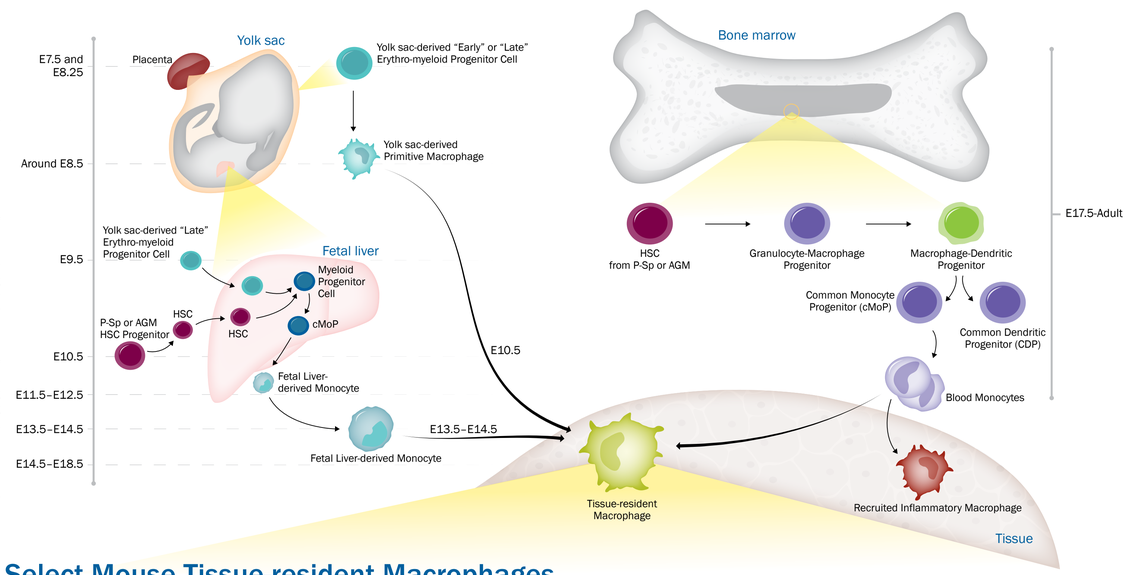
- Direct
- Antibody-dependent Cell-mediated Cytotoxicity



The Origins of Mouse Tissue-Resident Macrophages Redefined

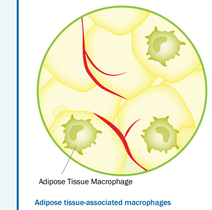
During development and throughout life, macrophages reside in many tissues of the body, contributing to both the maintenance of tissue homeostasis and the immune response following injury or pathogenic insult. In the late 1960s, van Furth and Cohn proposed that tissue-resident macrophages develop primarily from circulating, bone marrow-derived blood monocytes. This model was widely accepted until recent fate-mapping studies demonstrated that several tissue-resident macrophage populations in mice arise from HSC-independent embryonic precursors and are maintained by self-renewal. The earliest macrophages or primitive progenitors arise from early and late erythro-myeloid progenitors (EMPs) generated in the extra-embryonic yolk sac during primitive hematopoiesis at embryonic age 7.5 and 8.25 (E7.5 and E8.25). These EMPs can give rise to yolk sac-derived macrophages without passing through a monocytic intermediate and are the first to seed the fetal tissues following initiation of the blood circulation. With the exception of microglial cells in the brain, the primitive macrophages in most fetal tissues are subsequently replaced either partially or completely by fetal liver-derived monocytes. Fetal liver monocytes are generated from EMPs derived from either the yolk sac or hemogenic endothelium of the placenta and umbilical cord, or from hematopoietic stem cells (HSCs) generated in the para-aortic splanchnopleura (P-Sp) and aorta-gonad-mesonephros (AGM) regions of the embryo. These progenitors migrate to the fetal liver in two successive waves around E9.5 (EMPs) and E10.5/E11 (immature and mature HSCs) and expand, giving rise to fetal liver monocytes, which enter the circulation and differentiate into macrophages in peripheral tissues. In some tissues, including the liver, lung, skin, spleen, and peritoneum, fetal liver monocyte-derived macrophages maintain the ability to self-renew into adulthood and establish the tissue-resident population. In other tissues, such as the dermis and gut, fetal liver monocyte-derived macrophages are gradually replaced by the recruitment of bone marrow-derived monocytes generated from adult hematopoiesis beginning around E17.5.

Tissue-resident macrophages are a versatile, heterogeneous group of cells that support multiple tissue functions. Most of our knowledge about these cells has come from studies in mice, which suggest that the phenotypes and functional programs of tissue macrophages are determined by signals that they receive in their tissue microenvironments. Aside from providing the first line of defense against invading pathogens, tissue-resident macrophages have a fundamental role in maintaining tissue integrity and homeostasis. In addition, they may have specialized functions based on their locations and distinct gene expression profiles. For example, osteoclasts are bone-resident macrophages that specialize in bone resorption, while red pulp macrophages in the spleen specialize in heme degradation and iron recycling. Abnormalities in macrophage functions have been associated with a wide range of chronic inflammatory and autoimmune diseases including obesity and type II diabetes, asthma, atherosclerosis, fibrosis, cancer, inflammatory bowel disease, multiple sclerosis, and rheumatoid arthritis, suggesting that macrophages may serve as therapeutic targets. This possibility, however, requires a greater understanding of the differences in the development, phenotypes, and functions of tissue-resident macrophages.



Markers, Origins, & Specialized Functions of Select Mouse Tissue-resident Macrophages

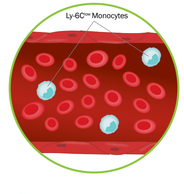
Adipose Tissue



Adipose tissue-associated macrophages
Markers:
CD45^{+}
F4/80^{+}
PPARγ^{+}

Adipose tissue-associated macrophages
Origin: Not clear
Specialized Functions: Adipogenesis; Adaptive thermogenesis; Regulation of insulin sensitivity and glucose tolerance
Associated Deficiencies or Pathologies: Obesity, insulin resistance, diabetes, loss of adaptive thermogenesis

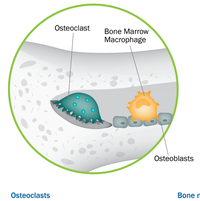
Blood



Ly-6C^{low} monocytes
Markers:
CD11b/Integrin αM^{high}
CD43^{+}
CX3CR1^{+}
F4/80^{+}
Ly-6C^{low}
M-CSF R/CD115^{+}
NGFI-Bα/Nur77/NR4A1^{+}

Ly6C^{low} monocytes
Origin: Bone marrow-derived monocytes
Specialized Functions: Immune surveillance; Maintenance of vascular integrity

Bone



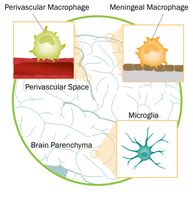
Osteoclasts
Markers:
Calcitonin Receptor^{+}
F4/80^{low}
RANK^{+}
NFATc1^{+}
Tartrate-resistant acid phosphatase (TRAP)$^{+}$

Bone marrow macrophages
Markers:
CD169^{+}
ER-HR3^{+}
F4/80^{+}
Tartrate-resistant acid phosphatase (TRAP)$^{-}$
VCAM-1/CD106^{+}

Osteoclasts
Origin: Presumed to be bone marrow-derived monocytes
Specialized Functions: Bone resorption and remodeling; Maintenance of the HSC niche
Associated Deficiencies or Pathologies: Osteopetrosis, osteoporosis, arthritis

Bone marrow macrophages
Origin: Yolk sac-derived or fetal liver-derived monocytes
Specialized Functions: Support erythropoiesis; Maintenance of the HSC niche
Associated Deficiencies or Pathologies: Disruption of hematopoiesis

Central Nervous System



Microglia
Markers:
AIF-1/Iba1^{+}
CD11b/Integrin αM^{+}
CD45^{low}
F4/80^{+}

Perivascular macrophages
Markers:
AIF-1/Iba1^{+}
CD11b/Integrin αM^{+}
CD45^{high}
CD163^{+}
F4/80^{+}
MMR/CD206^{+}
SR-A/MSR^{+}

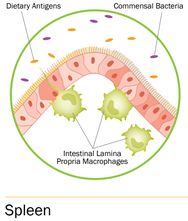
Meningeal macrophages
Markers:
AIF-1/Iba1^{+}
CD11b/Integrin αM^{+}
CD45^{high}
F4/80^{+}

Microglia
Origin: Yolk sac-derived
Specialized Functions: Brain development; Provision of neurotrophic factors; Removal of dead neurons and synaptic pruning
Associated Deficiencies or Pathologies: Neurodegeneration

Perivascular macrophages
Origin: Bone marrow-derived monocytes
Specialized Functions: Immune surveillance

Meningeal macrophages
Origin: Bone marrow-derived monocytes
Specialized Functions: Immune surveillance

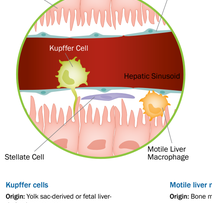
Gastrointestinal Tract



Intestinal lamina propria macrophages
Markers:
CD11b/Integrin αM^{+}
CD11c$^{med/+}$
CX3CR1^{high}
F4/80^{+}
Fcγ RI/CD64^{+}
MHC Class II^{high}

Intestinal lamina propria macrophages
Origin: Bone marrow-derived monocytes
Specialized Functions: Maintenance of intestinal homeostasis; Recognition and removal of intestinal pathogens; Maintenance of gut epithelial integrity
Associated Deficiencies or Pathologies: Inflammatory bowel disease

Liver



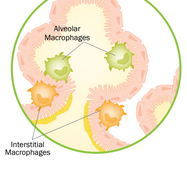
Kupffer cells
Markers:
B7-1/CD80$^{low/-}$
CD11b/Integrin αM^{low}
CD68/SR-D1^{+}
F4/80^{high}
Galectin-3/Mac-2^{+}
PPARγ^{+}
Siglec-1/CD169^{+}

Motile liver macrophages
Markers:
B7-1/CD80^{high}
CD11b/Integrin αM^{+}
F4/80^{+}

Kupffer cells
Origin: Yolk sac-derived or fetal liver-derived monocytes
Specialized Functions: Clearance of aged erythrocytes, blood-borne particles, toxins, and microorganisms; Tissue homeostasis and remodeling in the liver; Metabolic function in the liver
Associated Deficiencies or Pathologies: Hepatic fibrosis, fatty liver disease, non-alcoholic steatohepatitis, impaired erythrocyte clearance

Motile liver macrophages
Origin: Bone marrow-derived monocytes
Specialized Functions: Immune surveillance
Associated Deficiencies or Pathologies: Hepatic fibrosis, fatty liver disease, non-alcoholic steatohepatitis, impaired erythrocyte clearance

Lung



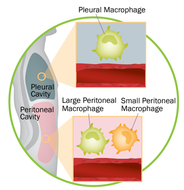
Alveolar macrophages
Markers:
CD11b/Integrin αM$^{low/-}$
CD11c^{high}
CD68/SR-D1^{+}
CD200 R1^{+}
DEC-205/CD205^{int}
Dectin-1^{+}
F4/80^{high}
Galectin-3/Mac-2^{+}
MARCO^{+}
MHC class II^{low}
MMR/CD206^{high}
PPARγ^{+}
Siglec-F^{high}

Interstitial macrophages
Markers:
CD11b/Integrin αM^{int}
CD11c^{-}
CD68/SR-D1^{+}
CD200 R1$^{+/-}$
F4/80^{+}
MHC class II$^{+/-}$
Siglec-F^{-}

Alveolar macrophages
Origin: Fetal liver-derived monocytes
Specialized Functions: Recycling of surfactant molecules; Immune surveillance of inhaled pathogens; Clearance of allergens, dust, and microorganisms
Associated Deficiencies or Pathologies: Pulmonary alveolar proteinosis

Interstitial macrophages
Origin: Fetal liver- and bone marrow-derived monocytes
Specialized Functions: Regulation of dendritic cell function

Serosal Tissues



Pleural macrophages
Markers:
CD11b/Integrin αM^{high}
F4/80^{high}
Tim-4^{+}

Large peritoneal macrophages
Markers:
CD11b/Integrin αM^{high}
CD11c^{low}
DC-SIGN/CD209^{-}
F4/80^{high}
GATA-6^{+}
MHC class II$^{low/-}$
L-Selectin/CD62L^{-}
Tim-4^{+}

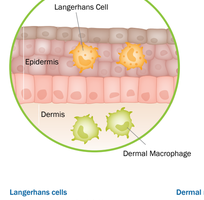
Small peritoneal macrophages
Markers:
CD11b/Integrin αM^{low}
CD11c^{-}
DC-SIGN/CD209^{-}
F4/80^{low}
MHC class II^{high}
L-Selectin/CD62L^{+}
Tim-4^{-}

Pleural macrophages
Origin: Bone marrow-derived monocytes
Specialized Functions: Immune surveillance

Large peritoneal macrophages
Origin: Yolk sac-derived or fetal liver-derived monocytes
Specialized Functions: Regulation of IgA production in the gut by peritoneal B1 cells

Small peritoneal macrophages
Origin: Bone marrow-derived monocytes
Specialized Functions: Immune surveillance

Skin



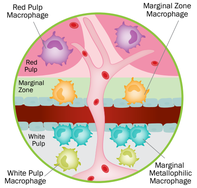
Langerhans cells
Markers:
CD11b/Integrin αM^{-}
CD11c^{+}
F4/80^{+}
Id2^{+}
Langerin^{+}
RUNX3/CBFA3^{+}

Dermal macrophages
Markers:
CD11b/Integrin αM^{+}
CD11c^{low}
CLEC10A/CD301^{+}
Dectin-1^{+}
Dectin-2^{+}
F4/80^{+}
Fcγ RI/CD64^{high}
MerTK^{+}
MHC class II^{low}
MMR/CD206^{-}
Siglec-1/CD169^{high}

Langerhans cells
Origin: Yolk sac-derived or fetal liver-derived monocytes
Specialized Functions: Immune surveillance
Associated Deficiencies or Pathologies: Defects in wound healing, fibrosis

Dermal macrophages
Origin: Bone marrow-derived monocytes
Specialized Functions: Immune surveillance

Spleen



Red pulp macrophages
Markers:
CD11b/Integrin αM^{low}
CD36/SR-B3^{+}
CD68/SR-D1^{+}
CD163^{+}
Dectin-2^{+}
F4/80^{+}
MMR/CD206^{+}
SIRPα/CD172a^{+}
Spi-C^{+}
VCAM-1/CD106^{+}

Marginal zone macrophages
Markers:
CD68/SR-D1^{+}
Dectin-2^{+}
F4/80^{low}
LXRα/NR1H3^{+}
MARCO^{+}
SIGNR1/CD209^{+}
TIM-4^{+}

Marginal metallophilic macrophages
Markers:
CD68/SR-D1^{+}
F4/80^{low}
LXRα/NR1H3^{+}
Siglec-1/CD169^{+}

White pulp (tingible body) macrophages
Markers:
CD68/SR-D1^{+}
MFG-E8^{+}
MerTK^{+}
TIM-4^{+}

Red pulp macrophages
Origin: Fetal liver-derived monocytes
Specialized Functions: Clearance of aged or damaged erythrocytes; Capture of blood-borne debris; Heme degradation; Iron recycling
Associated Deficiencies or Pathologies: Impaired iron homeostasis and erythrocyte clearance

Marginal zone macrophages
Origin: Bone marrow-derived monocytes
Specialized Functions: Clearance of pathogens present in the circulation; Retention of marginal zone B cells

Marginal metallophilic macrophages
Origin: Bone marrow-derived monocytes
Specialized Functions: Clearance of pathogens present in the circulation

White pulp macrophages
Specialized Functions: Clearance of apoptotic B cells

NOTE: This poster conveys a general overview and should be considered neither comprehensive nor definitive. The details of this information are understood to be subject to interpretation.

Models of Macrophage Activation

Following development, macrophages encounter diverse stimuli, which can alter their transcriptional programs leading to an activated state. The classic view of macrophage activation is described in a dichotomous model. According to this model, classical (M1) macrophage activation is induced by IFN-γ or lipopolysaccharide (LPS) and promotes a pro-inflammatory response, while alternative (M2) macrophage activation is induced by IL-4, IL-10, or IL-13 and stimulates an anti-inflammatory response. Slight phenotypic variations noted in the M2 phenotype, subsequently led to the description of different M2 subsets known as M2a, M2b, M2c, and M2d, which were defined based on the stimuli used for activation (top below). It has been widely recognized however, that even this expanded model of macrophage activation is too simplistic to account for the range of phenotypes observed in macrophages under different homeostatic and pathological conditions. For this reason, a new multidimensional model of macrophage activation has recently been proposed based on extensive gene expression analysis (bottom below). This model suggests that a spectrum of activation states spanning the M1/M2 states can occur in response to diverse signals including ontogeny-related signals, tissue-specific signals, and stress signals, which are integrated to determine the macrophage response.

Classical/Alternative Model of Macrophage Activation

M1 Markers

Cell Surface Markers
B7-1/CD80^{+}
B7-2/CD86^{+}
CD36/SR-B3^{+}
CD68/SR-D1^{+}
CD163^{-}
Fcγ RII/CD32^{+}
Fcγ RIII/CD16^{+}
IFN-γ R^{+}
MHC class II^{high}

Intracellular Markers
COX2^{+}
iNOS^{+}
IRF5^{+}
STAT1^{+}

Secreted Proteins
Cytokines
IL-1β^{+}
IL-6^{+}
IL-12^{high}
IL-15^{+}
IL-17^{+}
IL-18^{+}
IL-23^{+}
IFN-γ^{+}
TNF-α^{+}

Chemokines
CCL2–CCL5^{+}
CCL8^{+}
CCL11^{+}
CCL15^{+} (Human)
CCL19^{+}
CCL20^{+}
CXCL1–3^{+}
CXCL5^{+}
CXCL8–11^{+}
CXCL13^{+}
CCL16^{+}
CX3CL1^{+}

M1 Macrophage Functions:
Defense against pathogens

M1-Associated Pathologies:
Chronic inflammation, tissue damage, autoimmune disease

M2a Markers

Cell Surface Markers
CD163^{+}
CD200 R1^{+}
CLEC10A/CD301^{+}
CXCR1^{+}
CXCR2^{+}
DC-SIGN/CD209^{+}
Dectin-1^{+}
Fcε RIα^{+}
IL-1 RII^{+}
MHC class II^{low}
MMR/CD206^{+}

Intracellular Markers
Arginase 1^{+} (Mouse)
IRF4^{+}
PPARγ^{+}
STAT6^{+}

Secreted Proteins
Cytokines/Growth Factors
FIZZ1/RELMα^{+} (Mouse)
IL-1ra^{high}
IL-10^{high}
IL-12^{low}
TGF-β^{+}
Chemokines
CCL1^{+}
CCL2^{+}
CCL14^{+} (Human)
CCL17^{+}
CCL18^{+}
CCL22^{+}
CCL23^{+} (Human)
CCL24^{+}
CCL26^{+}
YM1/Chitinase 3-like 3^{+} (Mouse)

M2b Markers

Cell Surface Markers
B7-2/CD86^{+}
IL-4 Rα^{+}
MHC class II^{+}

Intracellular Markers
COX2^{+}
IRF4^{+}
SOCS3^{+}
SR-B1^{+}
TLR1^{+}

Secreted Proteins
Cytokines/Growth Factors
G-CSF^{+}
GM-CSF^{+}
IL-1β^{+}
IL-6^{+}
IL-10^{+}
TNF-α^{+}
Chemokines
CCL1^{+}
CCL20^{+}
CXCL1–CXCL3^{+}

M2 Macrophage Functions:
Wound healing & Tissue remodeling

M2-Associated Pathologies:
Cancer, fibrosis, epithelial hyperplasia

M2c Markers

Cell Surface Markers
CCR2^{+}
CD150/SLAM^{+}
CD163^{+}
IL-4 Rα^{+}
MMR/CD206^{+}
SR-A/MSR^{+}
SR-B1^{+}
TLR1^{+}

Intracellular Markers
Arginase 1^{+} (Mouse)
IRF4^{+}
SOCS3^{+}
TLR8^{+}

Secreted Proteins
Cytokines/Growth Factors
IL-10^{+}
TGF-β^{+}
Chemokines
CCL16^{+}
CCL18^{+} (Human)
CXCL13^{+}

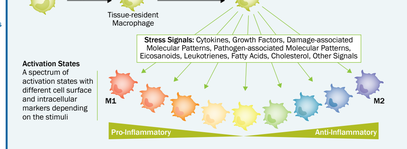
M2d Markers

Intracellular Markers
iNOS^{+}

Secreted Proteins
Cytokines/Growth Factors
IL-10^{+}
IL-12^{low}
VEGF^{+}

Chemokines
CCL5^{+}
CXCL10^{+}
CXCL16^{+}

New Multidimensional Model of Macrophage Activation



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