Arterial macrophage responses in cardiovascular health and disease

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Ottawa Heart Conference: Inflammation in Cardiometabolic disease

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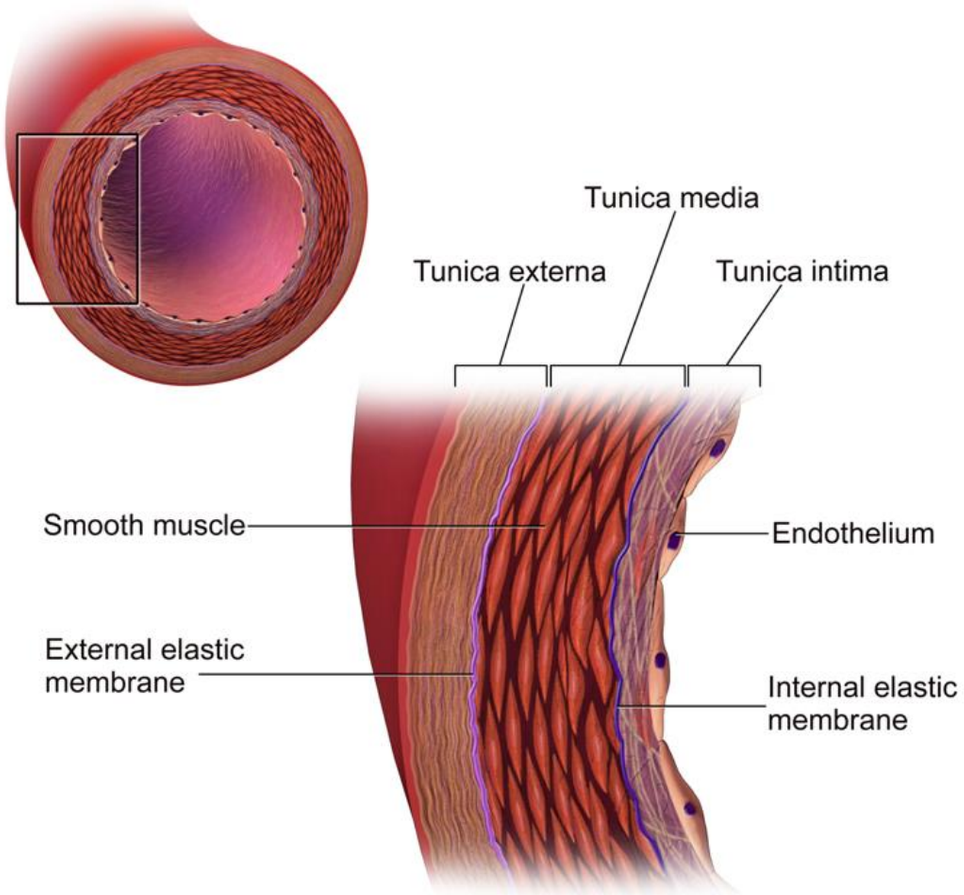
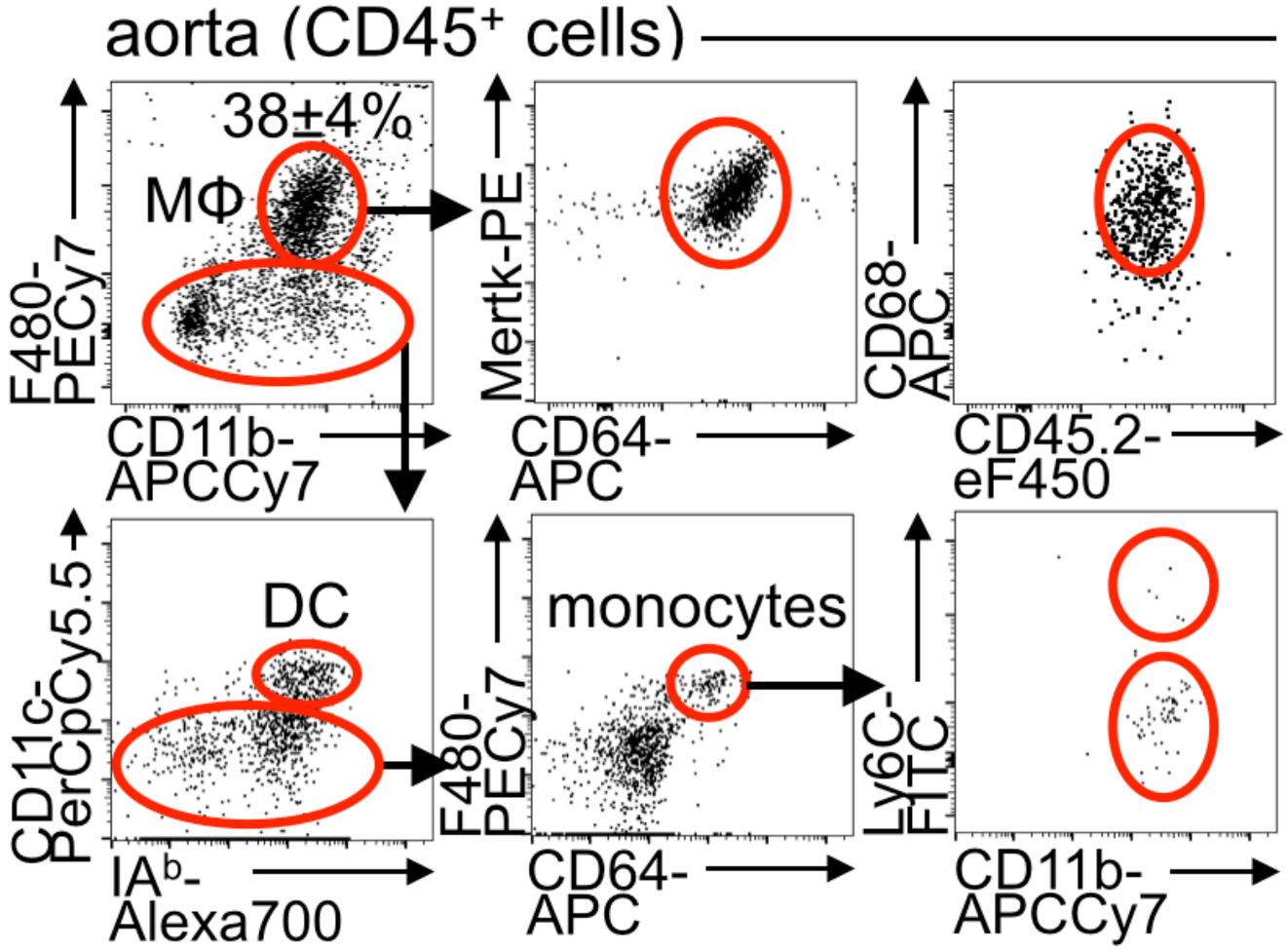
No disclosures

University of Toronto

UHN Toronto General Toronto Western Princess Margaret Toronto Rehab

The normal arterial wall is densely populated by tissue MΦ

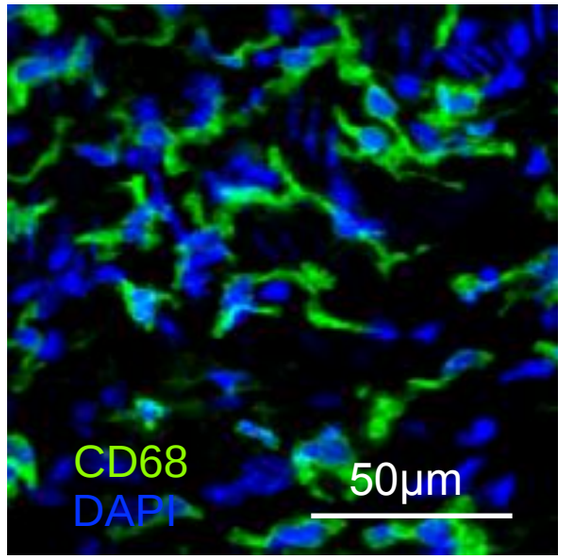




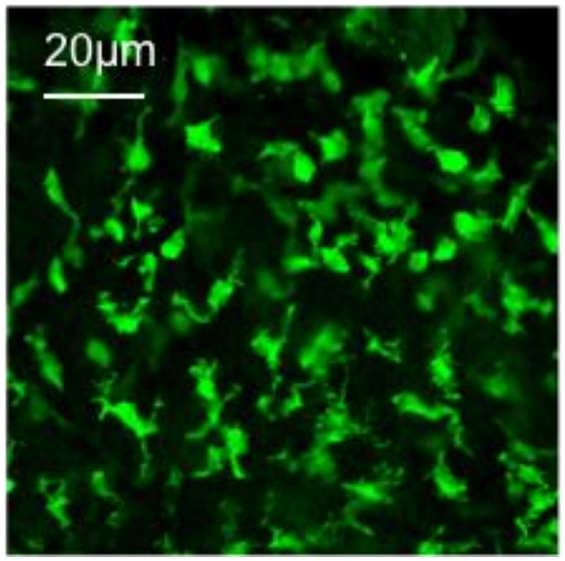
Ensan, Li, Besla *et al*. Nature Immunology 2016

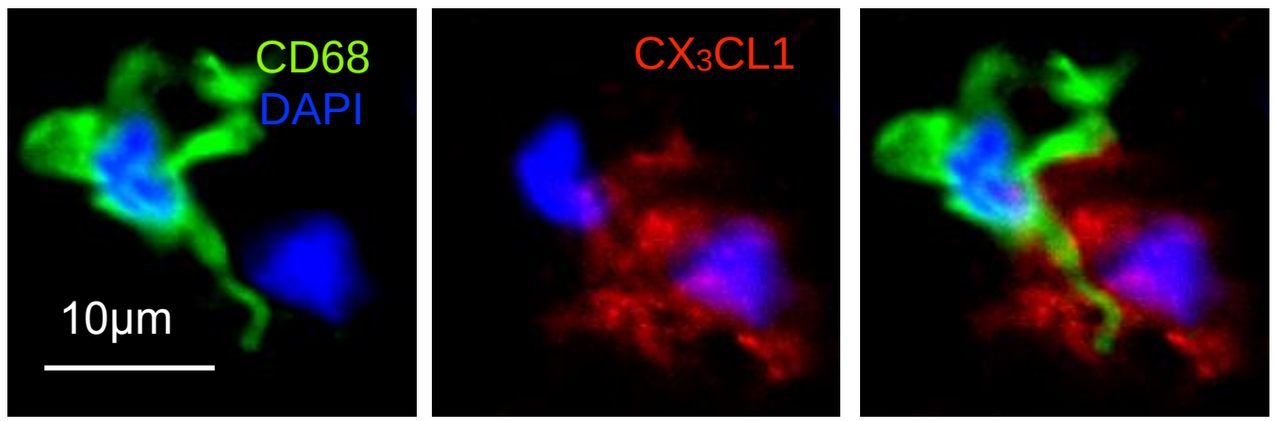
The normal arterial wall is densely populated by tissue MΦ

arterial adventitia

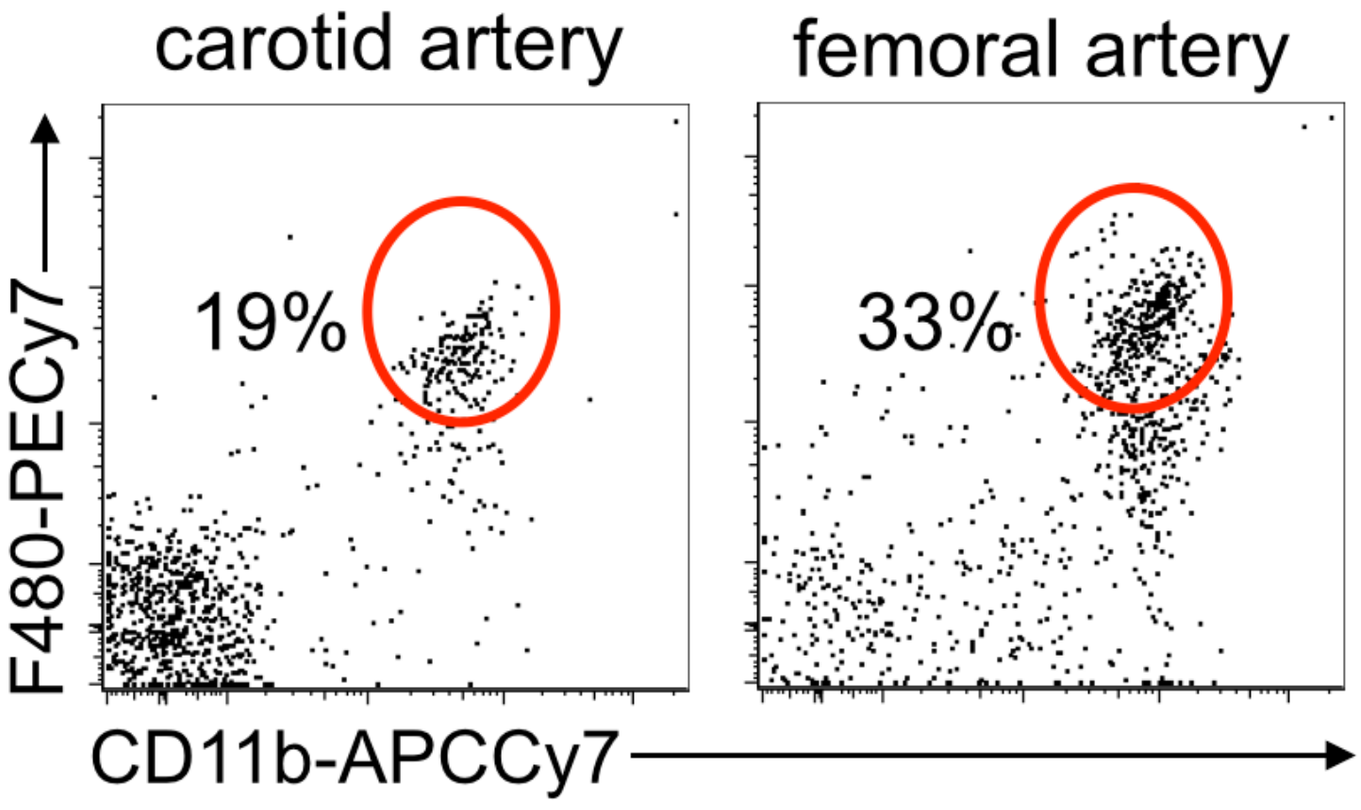


$CX_3CR1^{gfp/+}$ mice;
adventitia (adult)

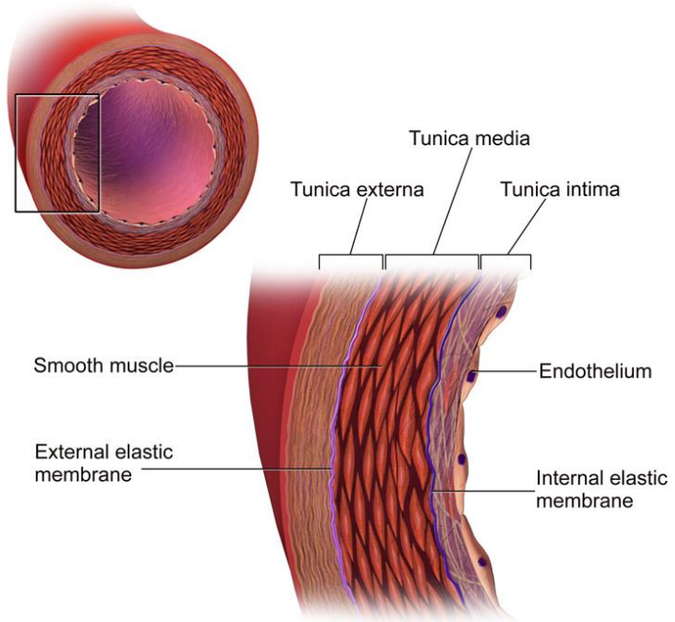


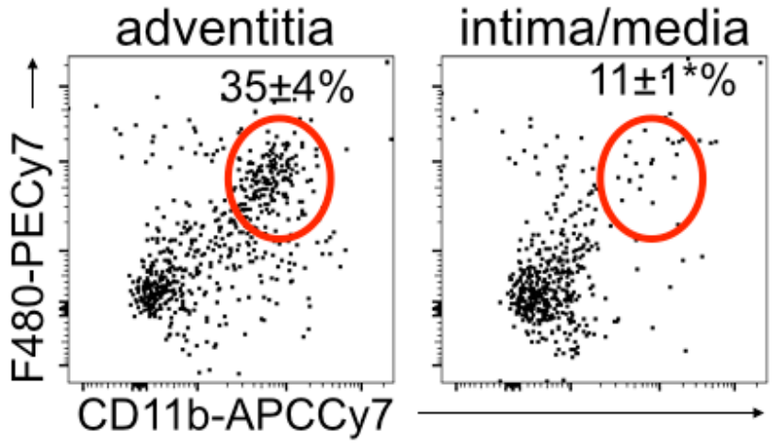


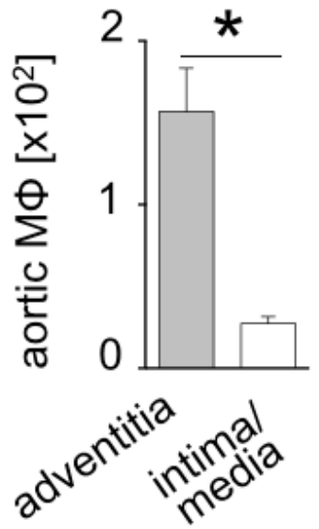
MΦ occupy multiple arterial sites.

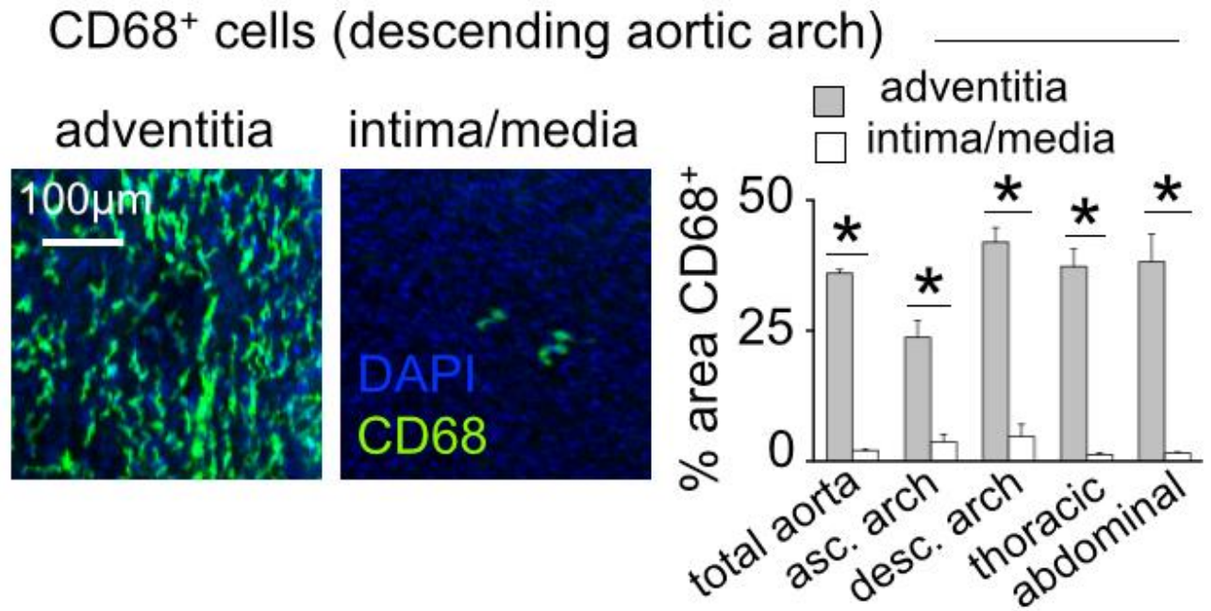


Spatial distribution of arterial MΦ









Ensan, Li, Besla *et al*. Nature Immunology 2016

Nat Immunol. 2016 Nov;17(11):1263-1272. doi: 10.1038/ni.3564. Epub 2016 Sep 26.

CCL19-CCR7-dependent reverse transendothelial migration of myeloid cells clears Chlamydia muridarum from the arterial intima.

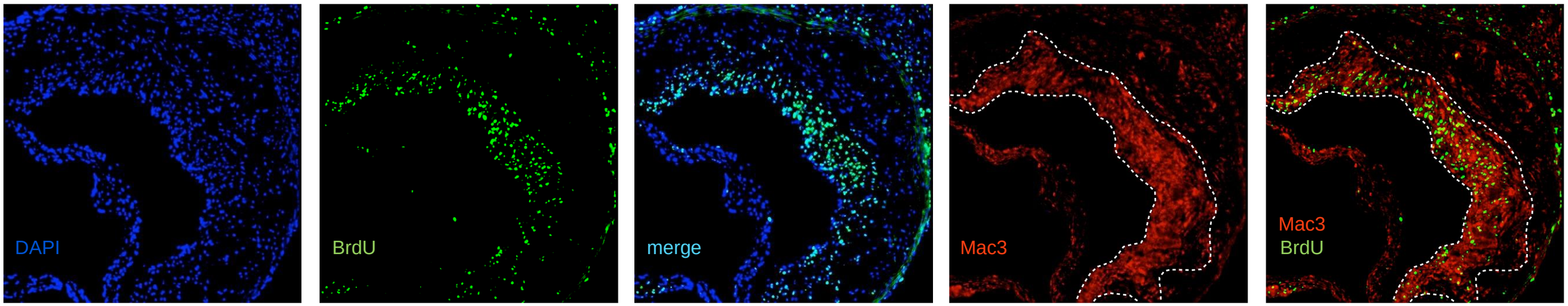
Roufaiel M[1,2], Gracey E[3,4], Siu A[1,2], Zhu SN[1], Lau A[1], Ibrahim H[1,2], Althagafi M[1,2], Tai K[1,4], Hyduk SJ[1], Cybulsky KO[1], Ensan S[1,4], Li A[1,4], Besla R[1,2], Becker HM[1,2,4], Xiao H[1], Luther SA[5], Inman RD[3,4,6], Robbins CS[1,2,4], Jongstra-Bilen J[1,2,4], Cybulsky MI[1,2,4].

⊕ Author information

Abstract

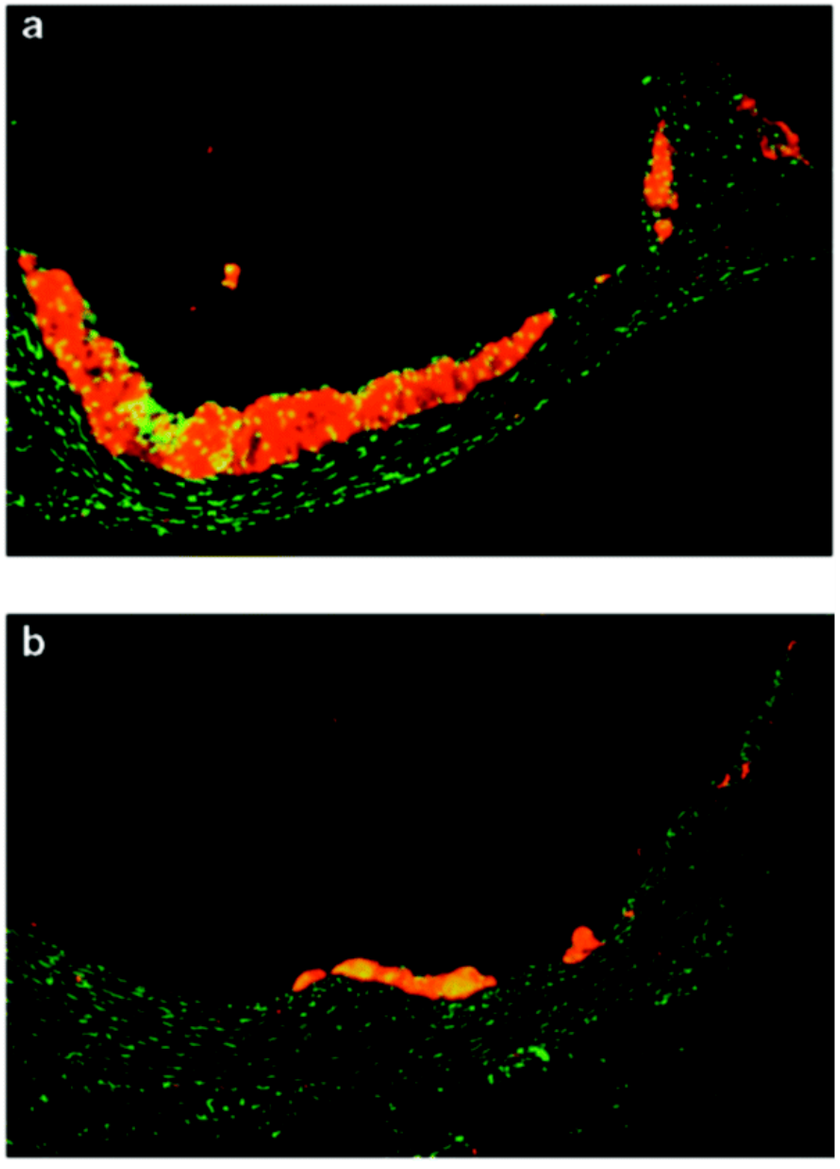
Regions of the normal arterial intima predisposed to atherosclerosis are sites of ongoing monocyte trafficking and also contain resident myeloid cells with features of dendritic cells. However, the pathophysiological roles of these cells are poorly understood. Here we found that intimal myeloid cells underwent reverse transendothelial migration (RTM) into the arterial circulation after systemic stimulation of pattern-recognition receptors (PRRs). This process was dependent on expression of the chemokine receptor CCR7 and its ligand CCL19 by intimal myeloid cells. In mice infected with the intracellular pathogen Chlamydia muridarum, blood monocytes disseminated infection to the intima. Subsequent CCL19-CCR7-dependent RTM was critical for the clearance of intimal C. muridarum. This process was inhibited by hypercholesterolemia. Thus, RTM protects the normal arterial intima, and compromised RTM during atherogenesis might contribute to the intracellular retention of pathogens in atherosclerotic lesions.

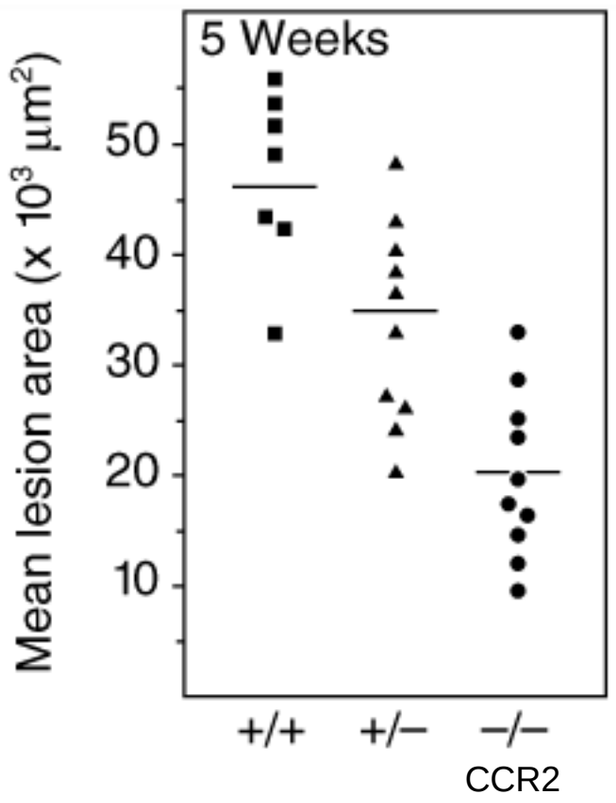
MΦ dominate inflammation in cardiovascular disease



Robbins, Hilgendorf *et al*. Nature Medicine 2013

MΦ depletion ameliorates cardiovascular disease





Boring *et al*. Nature 1998

Are all macrophages created equal?

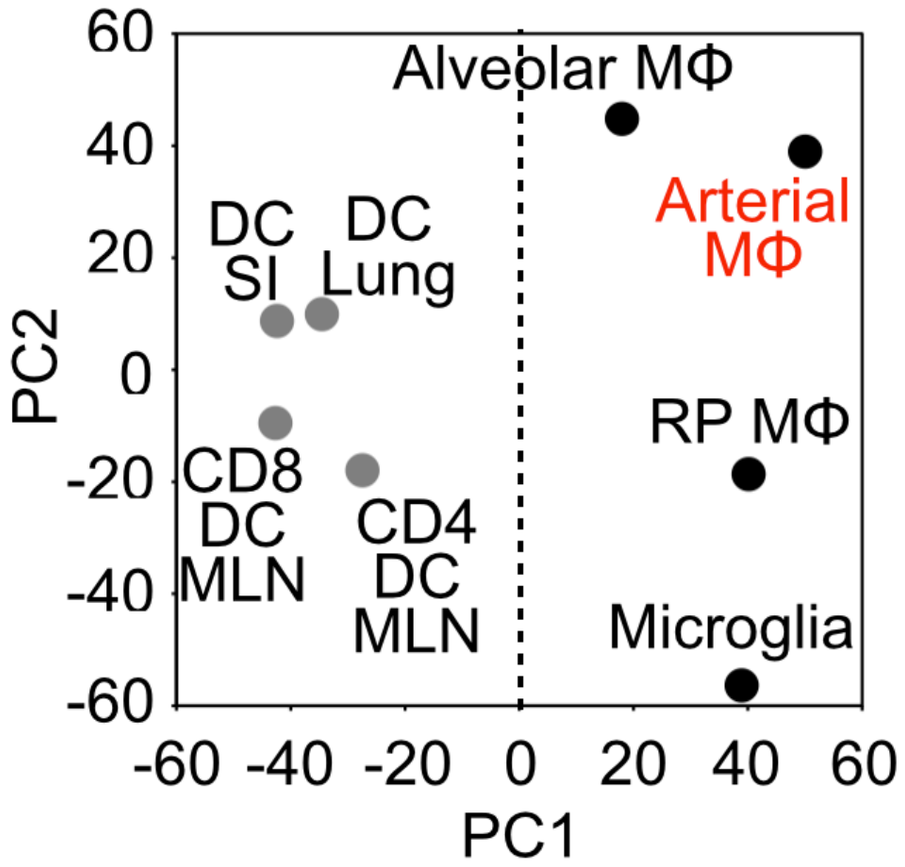
Diversity among tissue macrophages

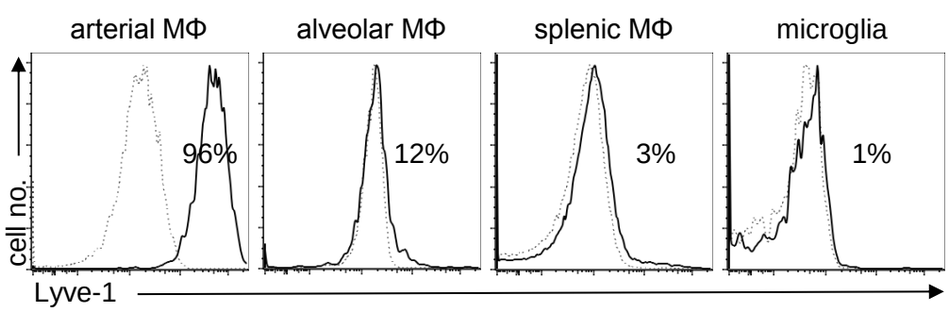
Table 1 Distinct locations and functions of tissue macrophages

Tissue	Cell type[a]	Functions and notes[b]	Phenotypic markers (tissue-selective transcriptional regulators[c])
Adipose tissue	'Adipose-associated macrophages'	Involved in control of insulin sensitivity[95] and adaptive thermogenesis[98]	F4/80$^+$, CD45$^+$ (white and brown adipose tissue)[98] (PPARγ[95])
Blood	Ly-6C^{lo} monocytes	Function analogously as 'intravascular housekeepers', clearing endothelial cell debris[114]	CX3CR1$^+$, Ly-6C^{lo}, F4/80$^+$, CSF1R$^+$ (ref. 114) (Nr4a1; ref. 114)
Bone	Osteoclasts	Multinucleated cells formed by fusion that resorb bone by disruption of the mineralized matrix[35]	Calcitonin receptor$^+$ (multinucleate)[116]
	Bone marrow macrophages	Support erythropoeisis[86,87] and maintain hematopoietic stem cells in stem cell niches[115]; this is an independent self-renewing population[29]	CD169$^+$, F4/80$^-$, ER-HR3$^+$ (ref. 117)
Central nervous system	Microglia	Promote neuronal survival and are involved in frontline immune surveillance, removal of dead neurons and synaptic remodelling[75,118]; derived from yolk sac and maintained in adult and during inflammation independently of the bone marrow[15,25,64]	F4/80$^+$, CD11b$^+$, CD45^{lo} (ref. 119)
	Perivascular macrophages	Immune surveillance	F4/80$^+$, CD11b$^+$, CD163$^+$, CD45^{hi} (ref. 119)
	Meningeal macrophages	Immune surveillance[119]	F4/80$^+$, CD11b$^+$, CD45^{hi} (ref. 119)
Gastrointestinal tract	Intestinal macrophages	Maintenance of intestinal homeostasis and regulation of immune responses to commensals[22,120]; monocyte-derived[22]	CX3CR1^{hi}, F4/80$^+$, CD11b$^+$, CD11c$^+$, CD64$^+$ (ref. 120)
Liver	Kupffer cells (sessile)	Clearance of microorganisms and cell debris from the blood, and clearance of aged erythrocytes[90,121]; prenatal origins[21]; maintained in the adult independently of the bone marrow[17]	F4/80^{hi}, CD11b^{lo}, CD169$^+$, CD68$^+$, Galectin-3$^+$ (ref. 122), CD80$^{lo/-}$ (ref. 121)[d] (PPARδ[97])
	Motile liver macrophages	Immune surveilance[121]	F4/80$^+$, CD11b$^+$, CD80^{hi} (ref. 121)
Lung	Alveolar macrophages	Immune surveillance of the lung for inhaled pathogens[50] and homeostatic regulation of tissue function[71,123], for example, clearance of surfactant; prenatal origins[21]; maintained in adult and during inflammation independently of the bone marrow[29,124]	F4/80^{lo}, CD11b^{lo}, CD11c^{hi}, CD68$^+$, Siglec F$^+$, MARCO$^+$, CD206$^+$, Dectin-1$^+$ (ref. 126), Galectin-3$^+$[122] (PPARγ[71])
	Interstitial macrophages	Regulates DC maturation and/or activation[125]	F4/80$^+$, CD11c$^-$, CD68$^+$, MHC II$^+$ (ref. 125)
Serosal tissues	Peritoneal macrophages:		
	F4/80^{hi} majority	Immune surveillance and regulation of homeostatic environment[49,127]; apoptotic cell clearance[79]; prenatal origins[21]; maintained in adult and during inflammation independently of the bone marrow[21,28]	F4/80^{hi}, CD11b^{hi}, Tim4$^+$ (ref. 82)[d], MHCII^{lo}
	F4/80^{lo}		F4/80^{lo}, CD11b$^+$, Tim4$^-$, MHCII^{hi}, CD11c$^{+/-}$ (this population is most likely heterogeneous, mixed with dendritic cells)
	Pleural macrophages:		
	F4/80^{hi} majority	Immune surveillance[128]; maintained in adult and can expand during T_H2 cell inflammation independently of the bone marrow[40]	F4/80^{hi}, CD11b^{hi}, Tim4$^+$ [(d)]
	F4/80^{lo}		F4/80^{lo}, CD11b$^+$, Tim4$^-$ (dendritic cell–macrophage content undetermined; unpublished observations)
Skin	Dermal macrophages	Immune surveillance[129]	F4/80$^+$, CD11b$^+$, CD11c^{lo}, CD206$^+$, MHCII^{lo}, CD169$^+$ (In the deep dermis)[122], Dectin-1$^+$, CD301$^+$ (ref. 131), Dectin-2$^+$ (ref. 132)
	Langerhans cells	Interaction with T lymphocytes[130]; derived from yolk sac and/or fetal liver and maintained independently of the bone marrow[14,16]	F4/80$^+$, CD11b$^+$, CD11c$^+$, Langerin$^+$[14] (Id2 (ref. 133) and Runx3 (ref. 134))
Spleen	Marginal zone macrophages	Immune surveillance of the circulation[101]	CD68$^+$, CD209b$^+$, MARCO$^+$, Dectin-2$^+$ (ref. 132), Tim4$^+$ (ref. 108), (LXRα[108])
	Metallophilic macrophages	Immune surveillance[101]	CD68$^+$, CD169$^+$ (ref. 101) (LXRα[108])
	Red pulp macrophages	Erythrocyte clearance and iron metabolism[102]; prenatal origins[17,21]; maintained in adult independently of the bone marrow[29]	F4/80$^+$, CD206$^+$, Dectin-2$^+$ (ref. 132), Spi-C[102]
	White pulp (tingible body) macrophages	Clearance of apoptotic cells resulting during the germinal center reaction[99]	CD68$^+$ (ref. 101)

[a]This table is a simplification; marked heterogeneity is evident in many tissues (for example, bone marrow, peritoneum, lung and liver) highlighted through fate mapping studies and phenotypic variation[17,21,32,121,127]. [b]Origin is indicated only where experimentally established. [c]Select examples of tissue-selective transcriptional regulators involved in cellular development or function are indicated. [d]Marker is expressed by the majority of the indicated cells. Subsets are only listed where distinct anatomical localization, function or origins are reported, and not those that are simply defined by variation in select receptor or antigen expression.

Diversity among tissue macrophages





Ensan, Li, Besla *et al*. Nature Immunology 2016

Macrophage Origins

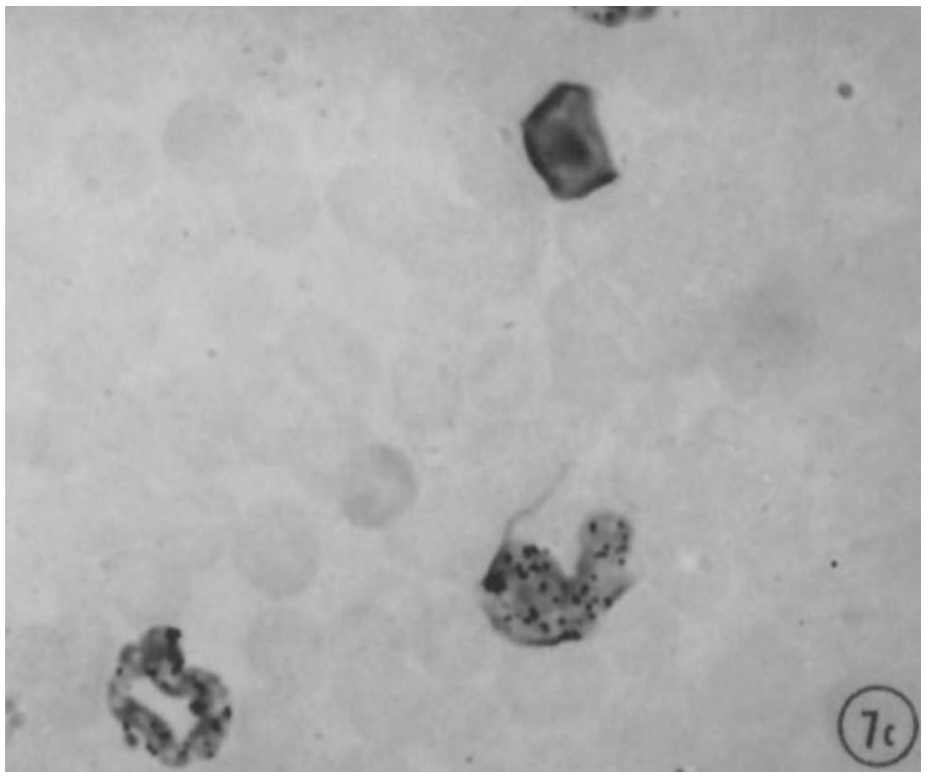
(beyond environmental influences)

THE ORIGIN AND KINETICS OF MONONUCLEAR PHAGOCYTES

By RALPH VAN FURTH,* M.D., AND ZANVIL A. COHN, M.D.

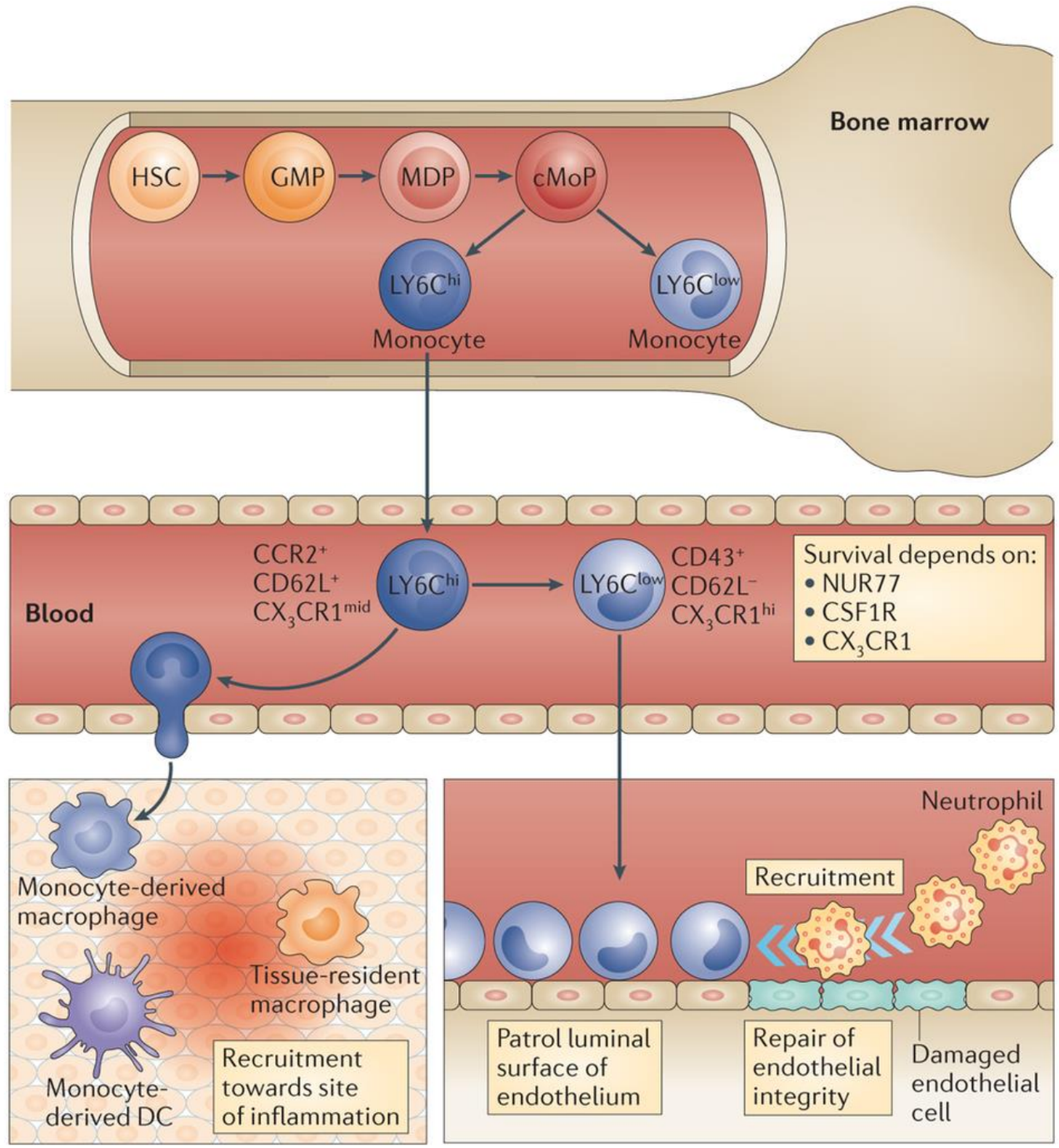
(*From The Rockefeller University, New York 10021*)

(Received for publication 8 May 1968)



On the basis of these studies the life history of mouse mononuclear phagocytes was formulated to be: *promonocytes* in the bone marrow, → *monocytes* in the peripheral blood, → *macrophages* in the tissue.

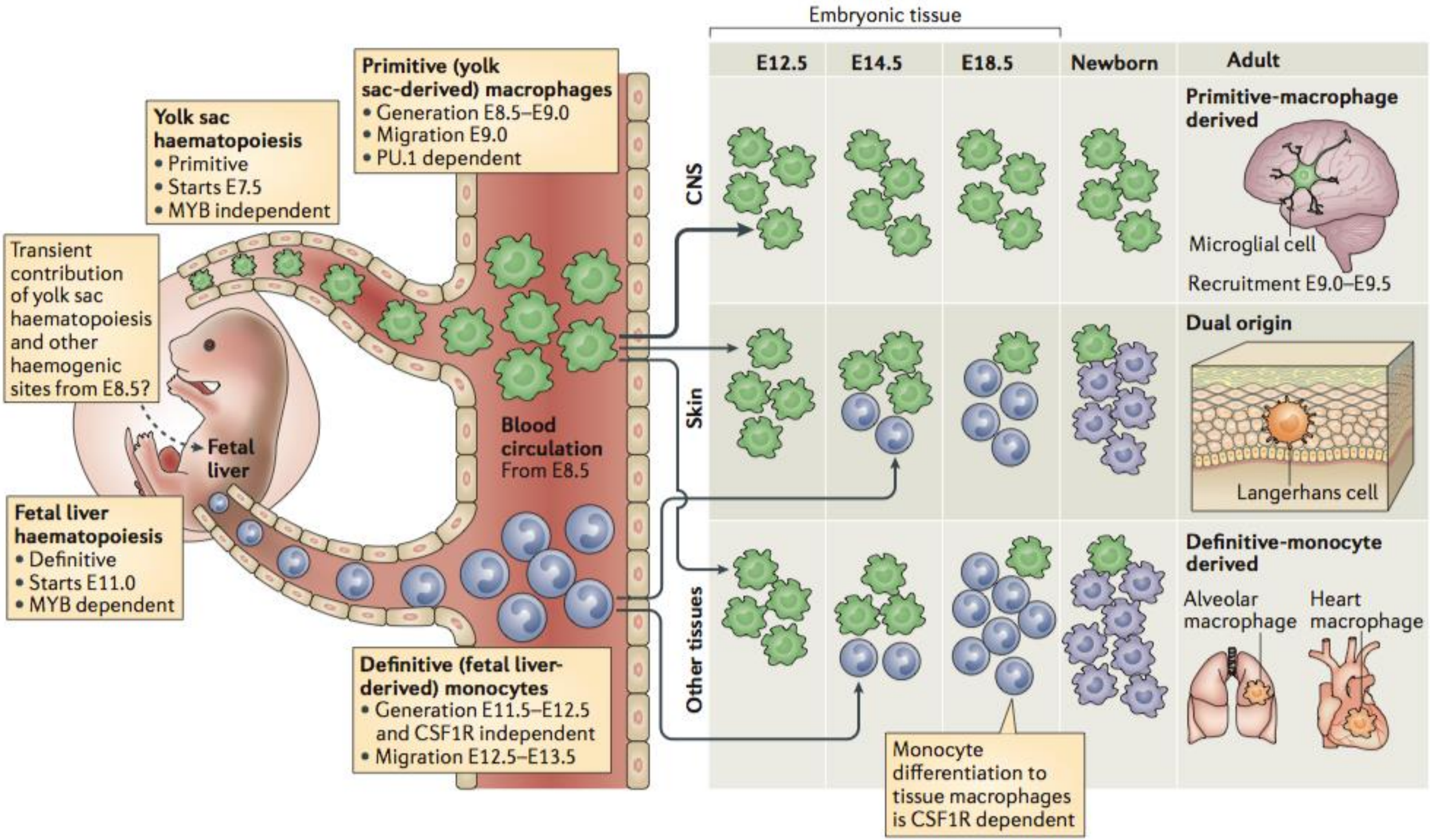
The mouse monocyte compartment



Nature Reviews | **Immunology**

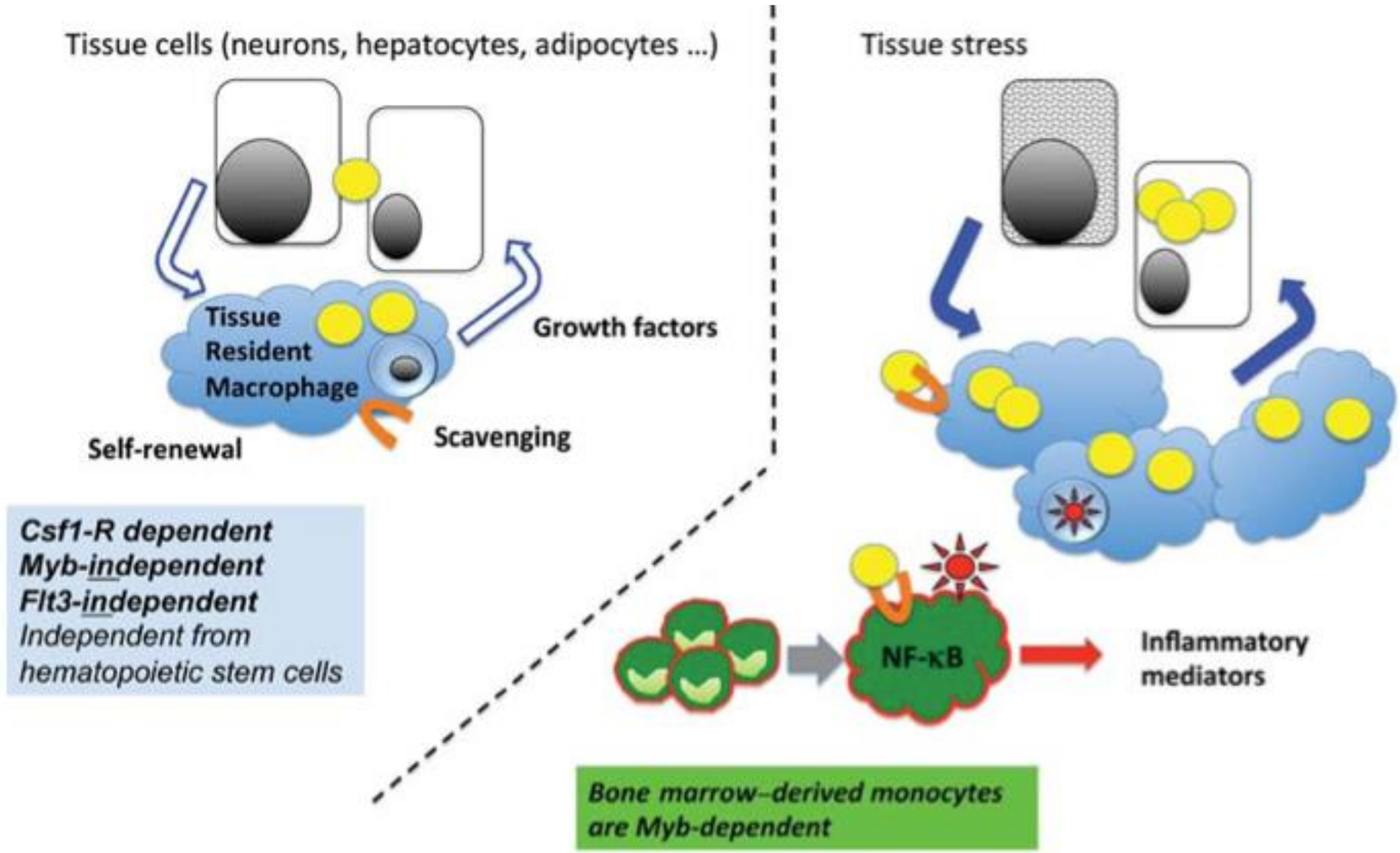
Nature Reviews Immunology **14**, 392–404 (2014)

Embryonic MΦ development



Ginhoux et al. *Nat Rev Imm* **14**, 392–404 (2014).

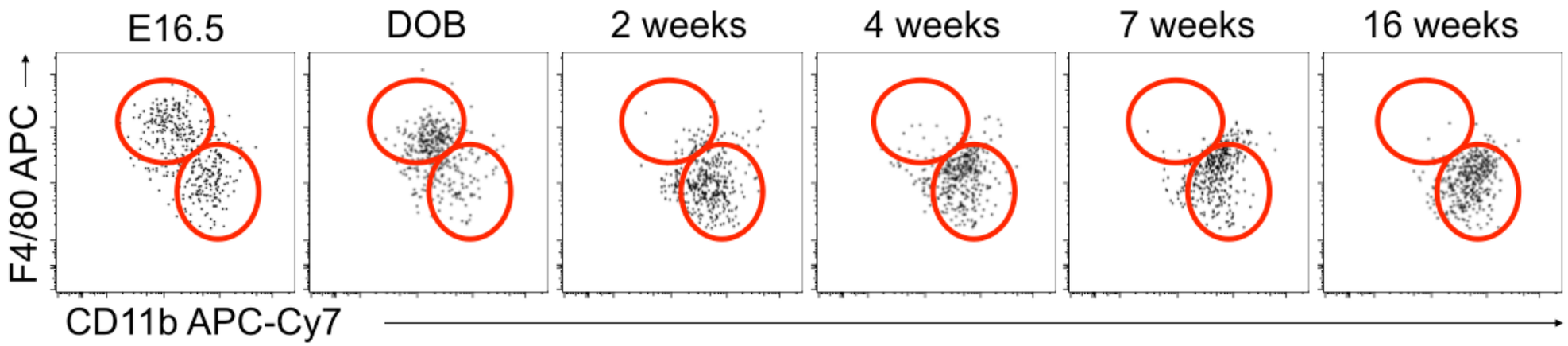
Functional differences between bone marrow dependent and independent macrophage networks



Perdiguero and Geissmann *CSH Symposia* 2013

Arterial Macrophage Origins

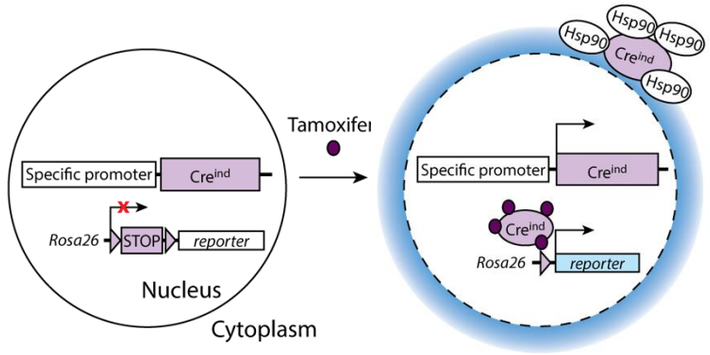
Embryonic origins of arterial macrophages

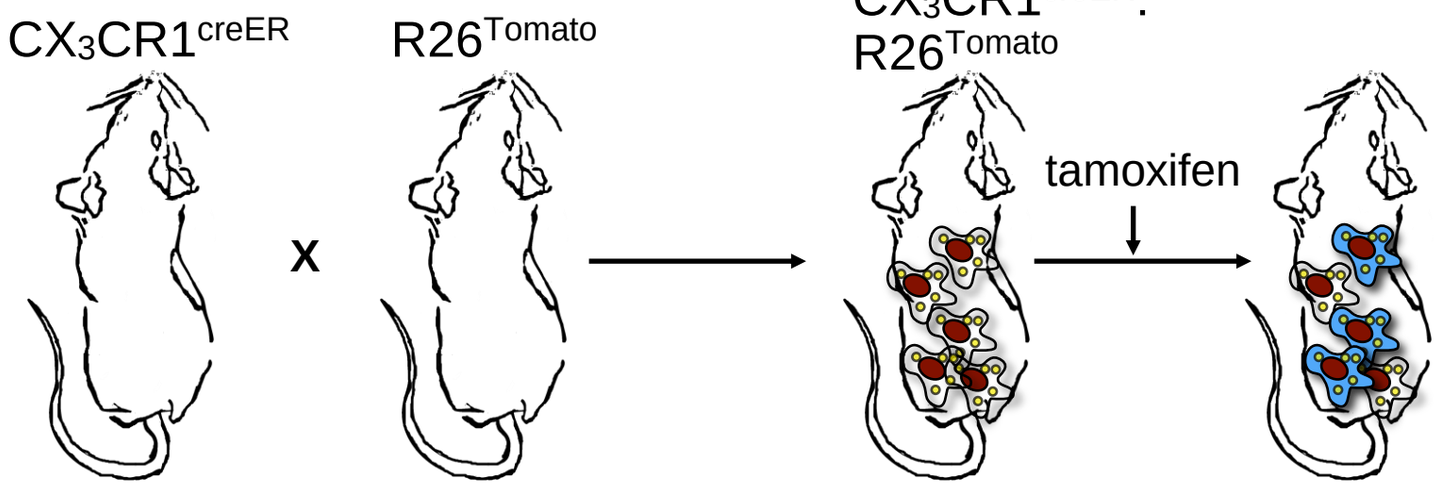


Ensan, Li, Besla *et al*. Nature Immunology 2016

Embryonic origins of macrophages: Lineage Tracing

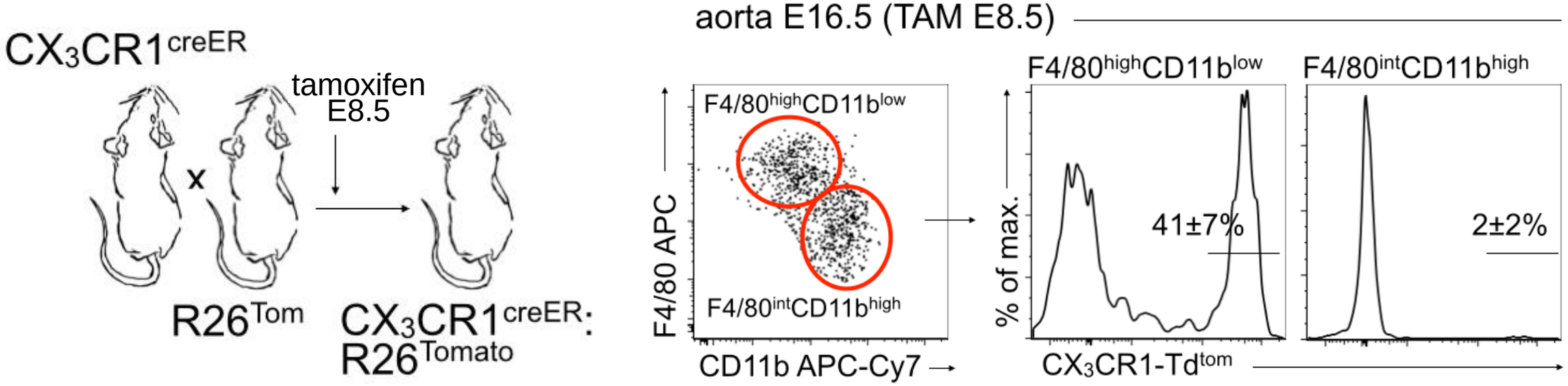
Adapted from Hofer *et al*. Annu Rev Immunol. 2016





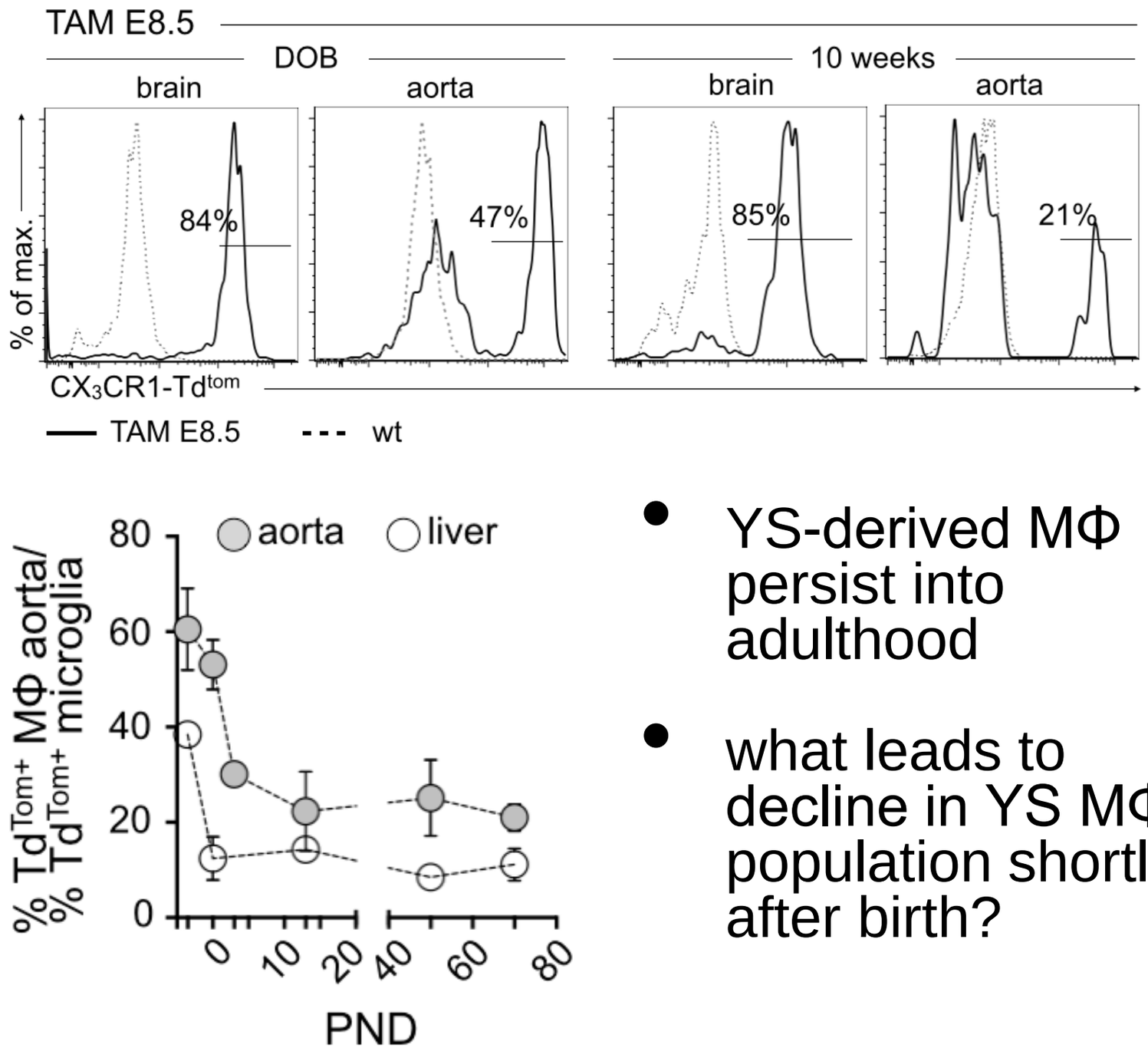
- pulse-label CX_3CR1-expressing progenitor cells in the yolk sac, fetal liver, etc.
- tamoxifen-induced expression of Cre recombinase under control of CX_3CR1 promoter

YS progenitor contribution to arterial MΦ development



Ensan, Li, Besla *et al*. Nature Immunology 2016

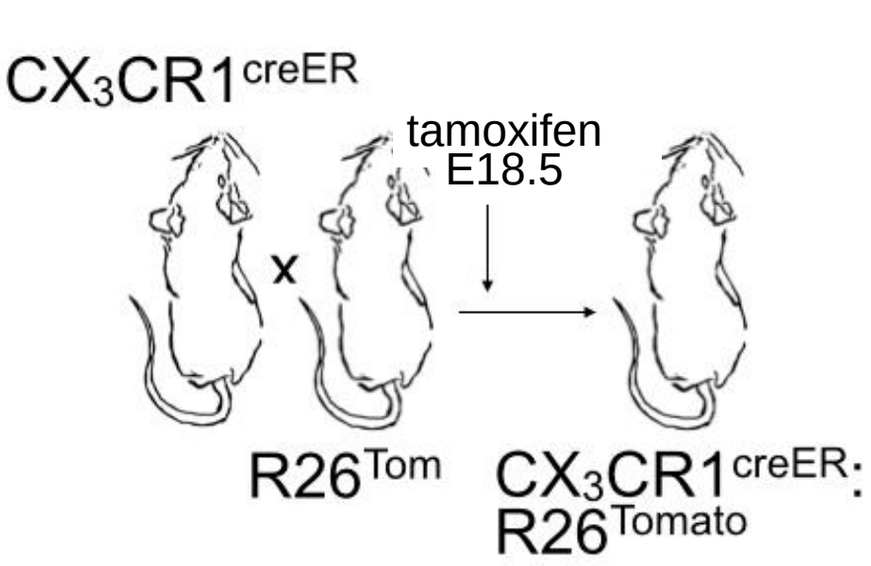
Contribution of YS-derived progenitors to adult arterial MΦ pool

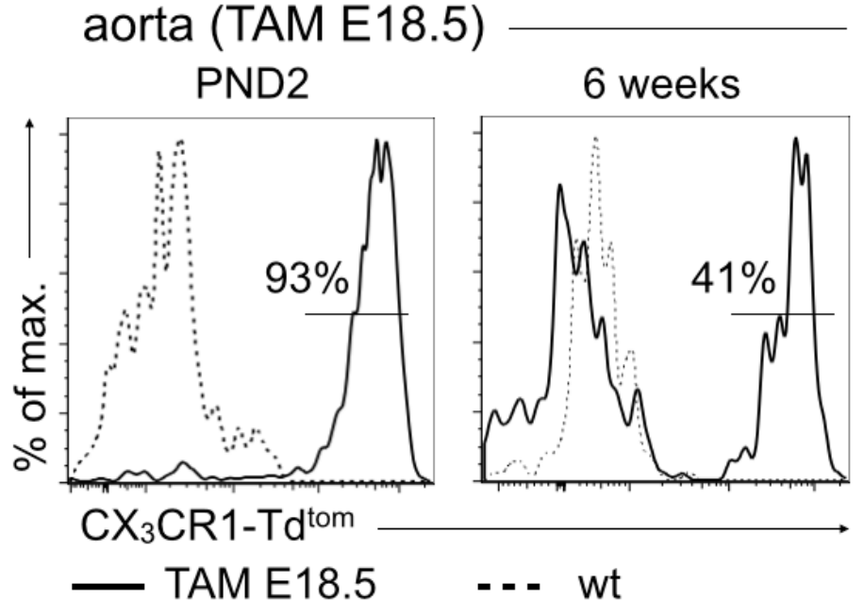


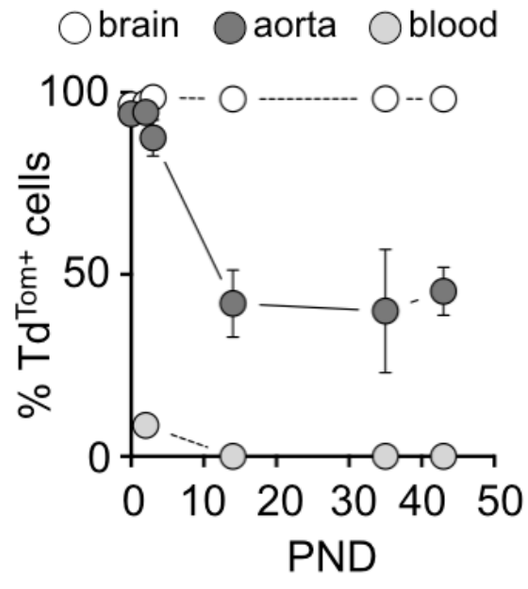
- YS-derived MΦ persist into adulthood
- what leads to decline in YS MΦ population shortly after birth?

Ensan, Li, Besla *et al*. Nature Immunology 2016

Arterial MΦ colonization associates with a brief post natal period of monocyte recruitment

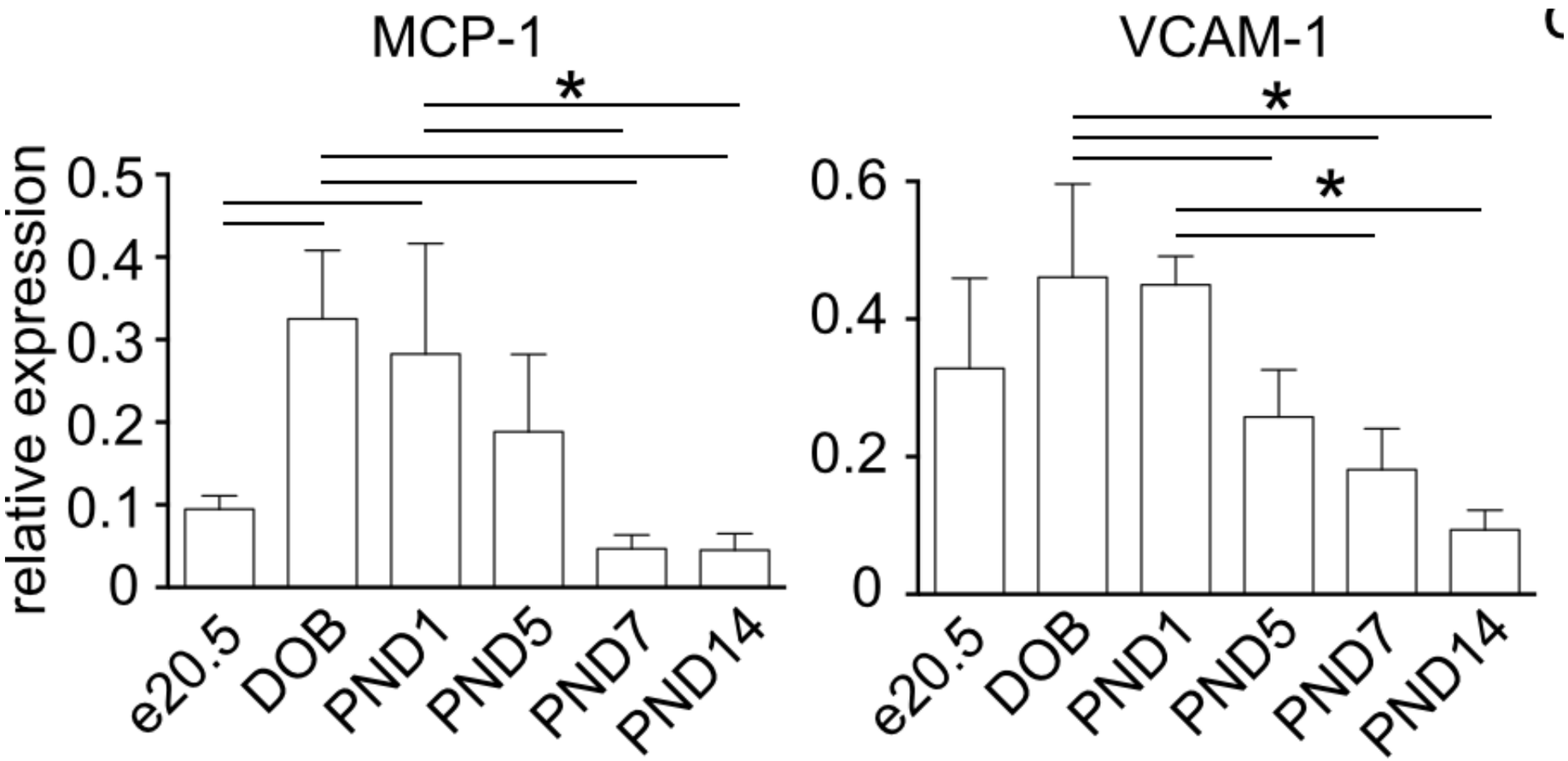






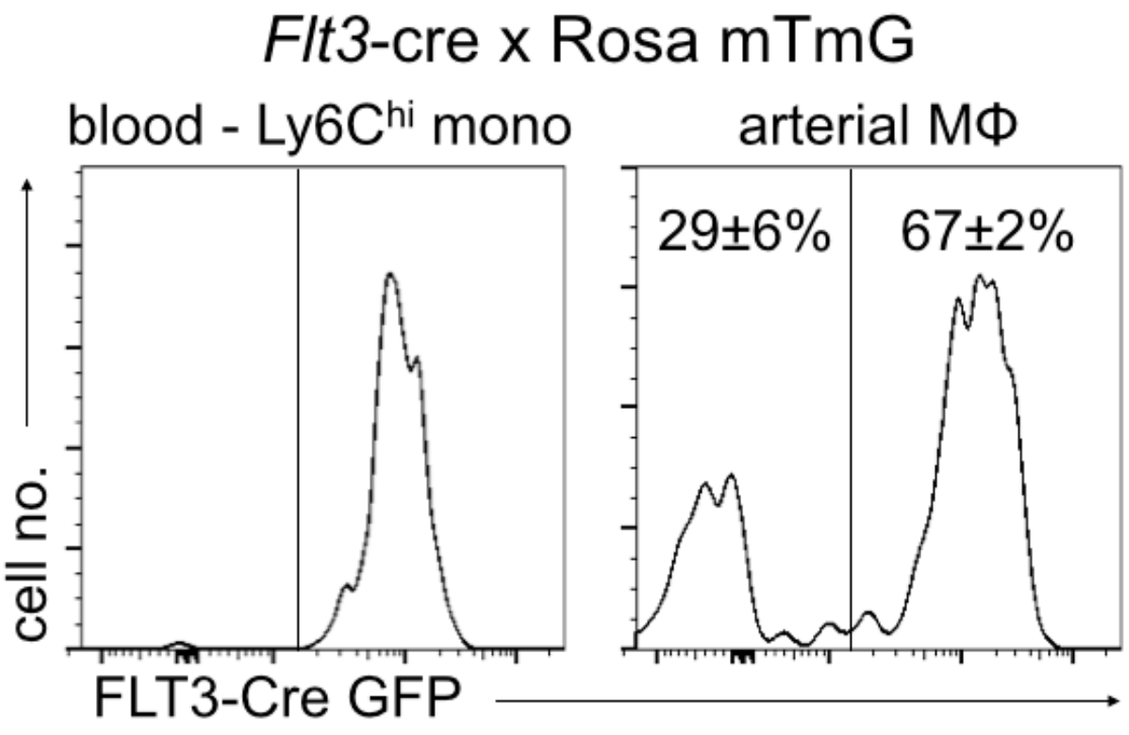
Ensan, Li, Besla *et al*. Nature Immunology 2016

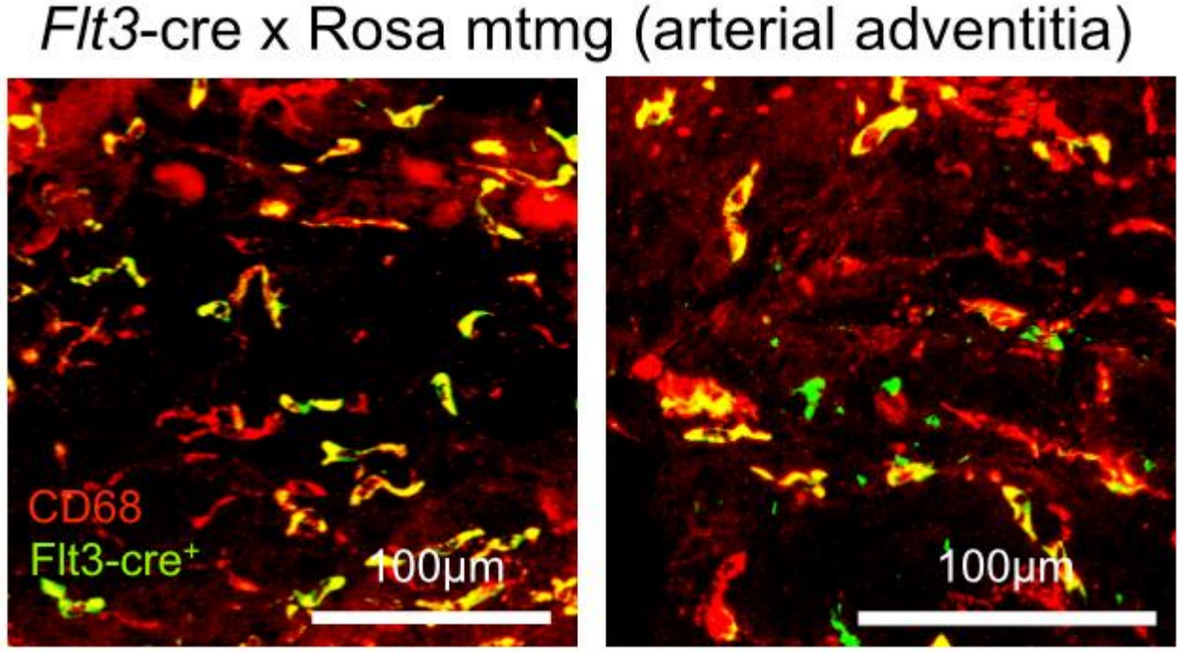
Monocyte accumulation is associated with increased arterial expression of chemotactic factors and adhesion molecules



Ensan, Li, Besla *et al*. Nature Immunology 2016

Arterial MΦ colonization associates with a brief post natal period of monocyte recruitment

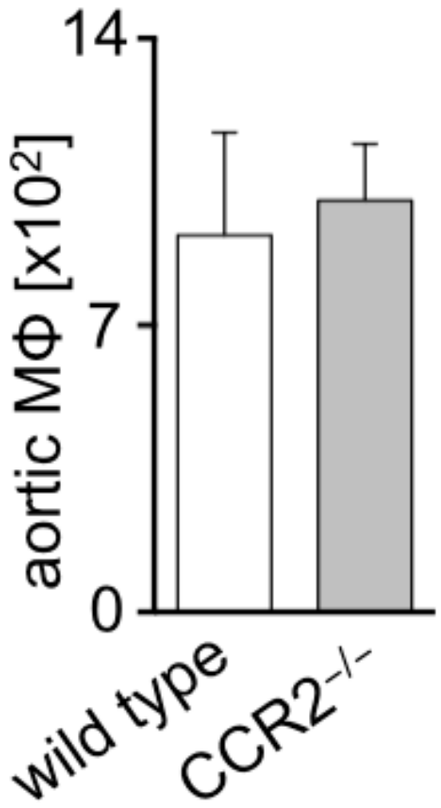




Ensan, Li, Besla *et al*. Nature Immunology 2016

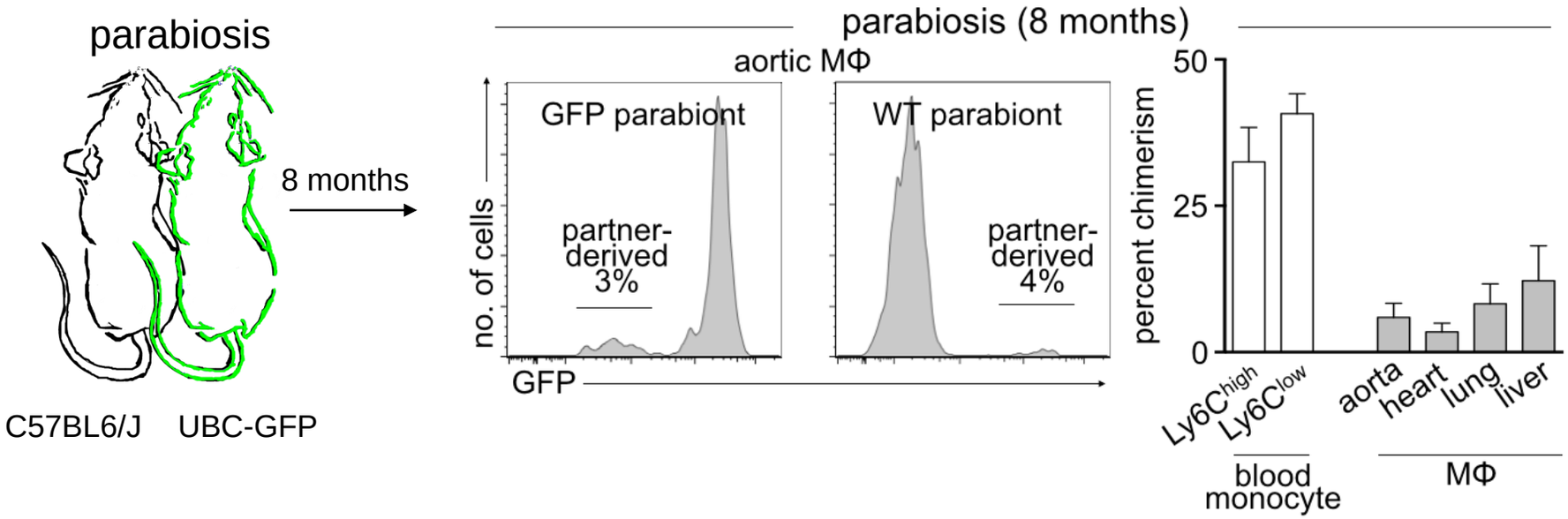
What maintains arterial MΦ abundance in adulthood?

Maintenance of arterial MΦ in adulthood occurs largely independent of circulating monocytes



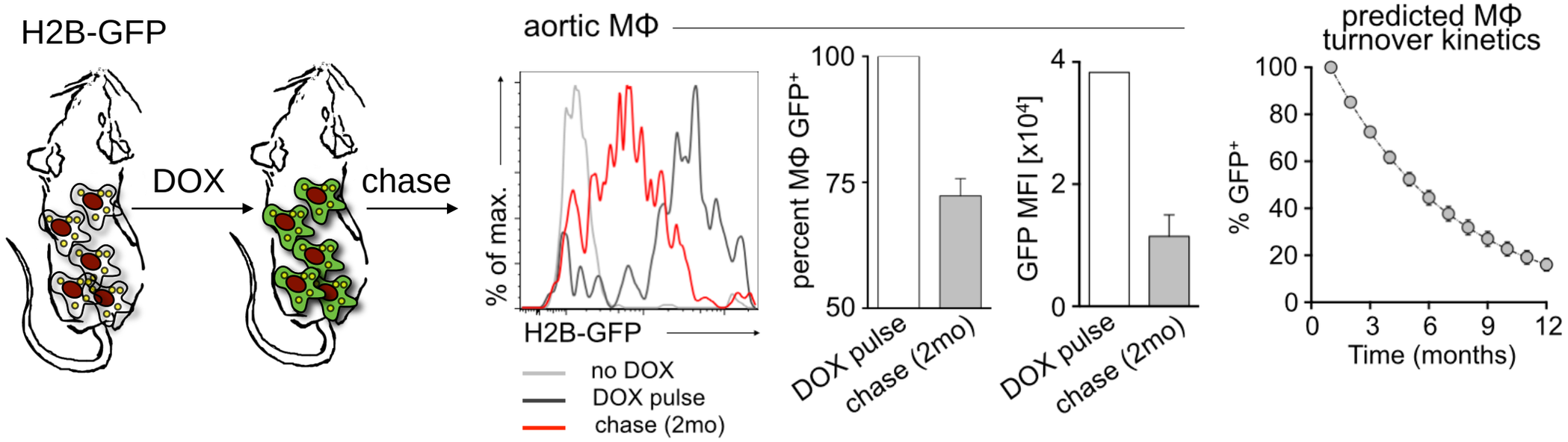
Ensan, Li, Besla *et al*. Nature Immunology 2016

Maintenance of arterial MΦ in adulthood occurs largely independent of circulating monocytes



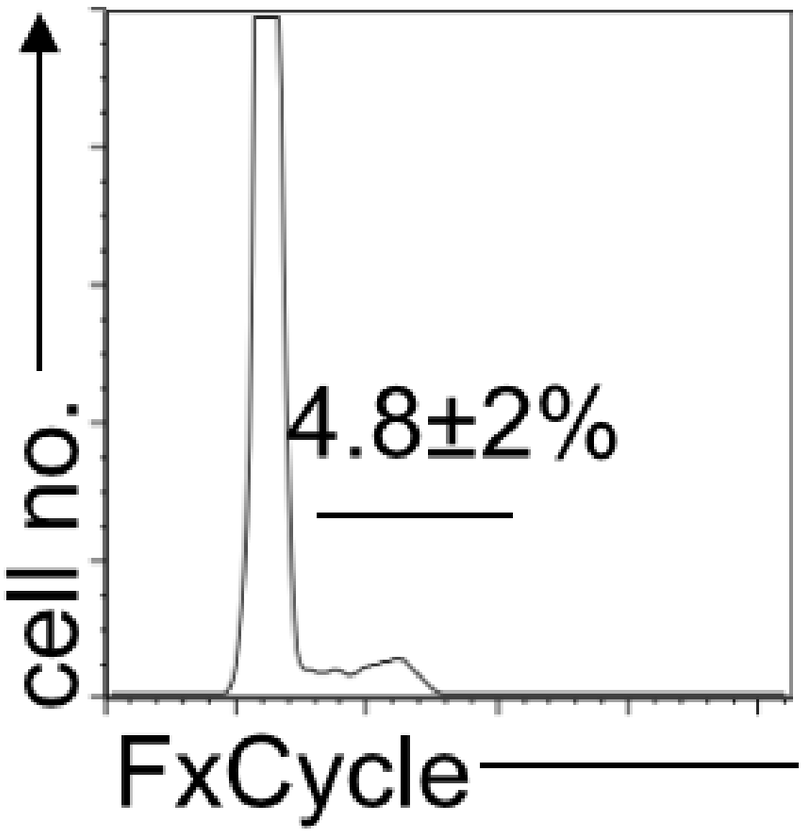
Ensan, Li, Besla *et al*. Nature Immunology 2016

Arterial MΦ turnover kinetics



Ensan, Li, Besla *et al*. Nature Immunology 2016

Tissue MΦ renew through local proliferation

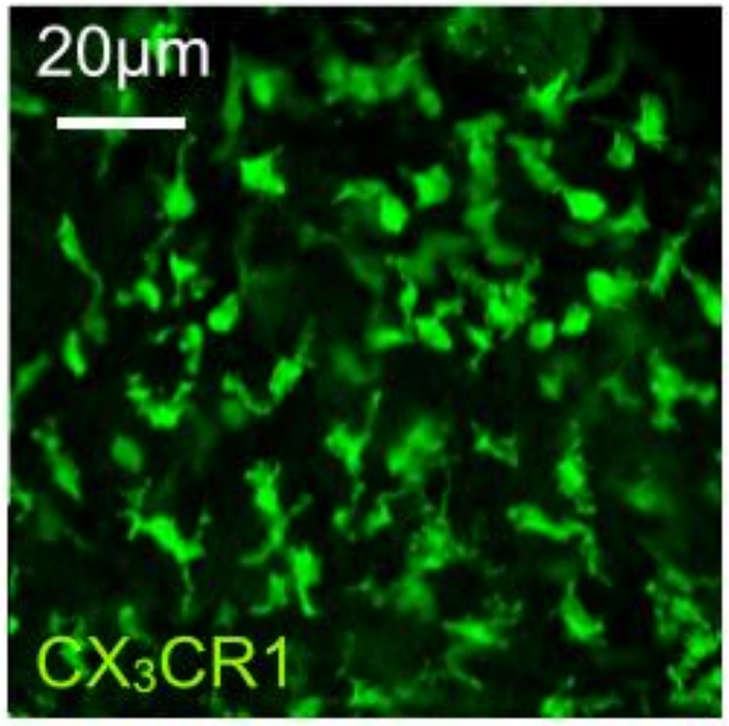


Ensan, Li, Besla *et al*. Nature Immunology 2016

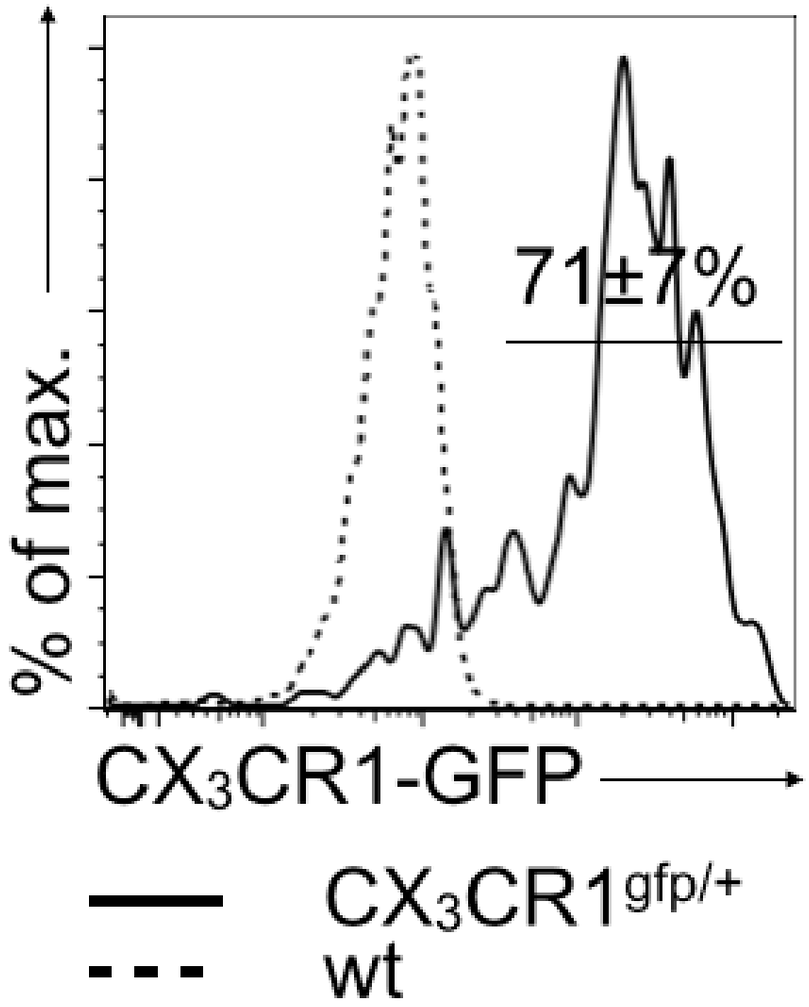
Arterial MΦ survival

CX_3CR1 expression on arterial MΦ persists into adulthood

$CX_3CR1^{gfp/+}$ mice; adventitia (adult)



(CD45+F4/80+ CD11b+cells)



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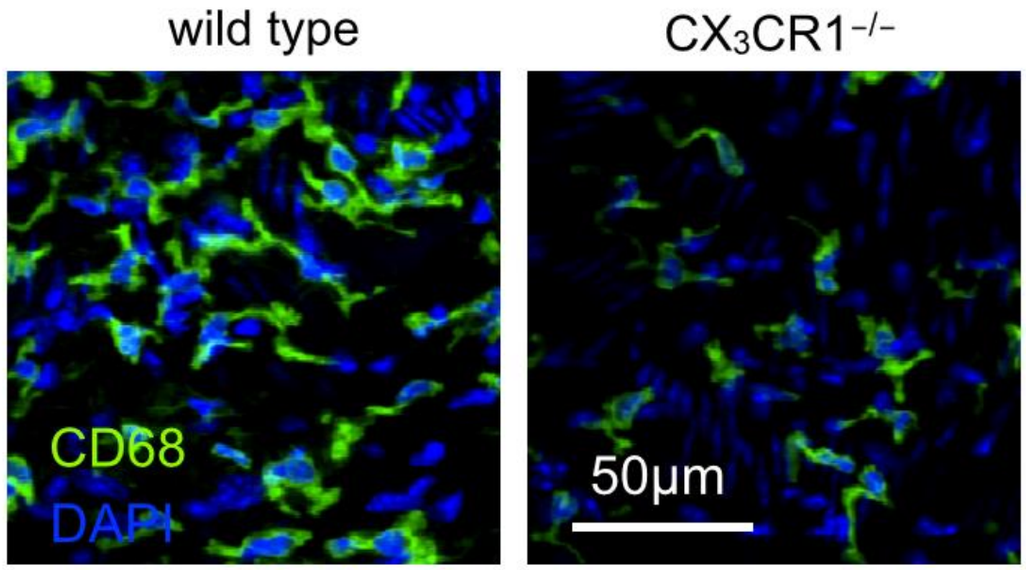
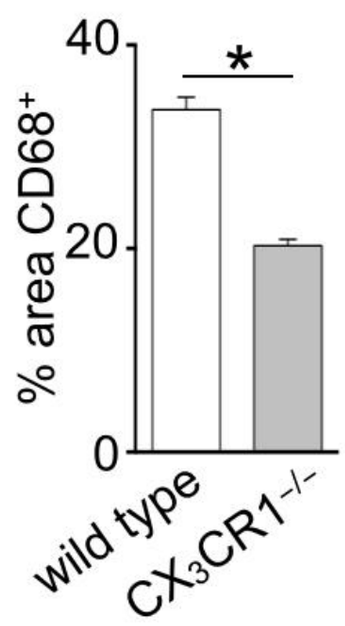
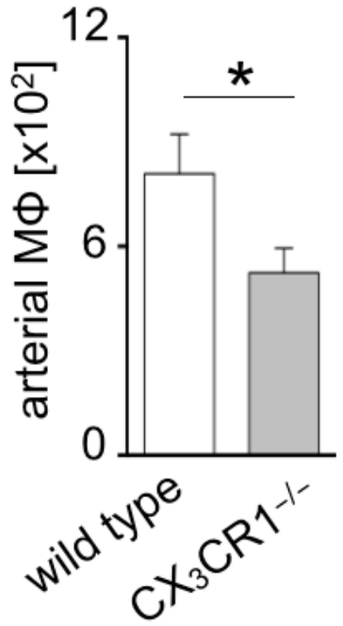
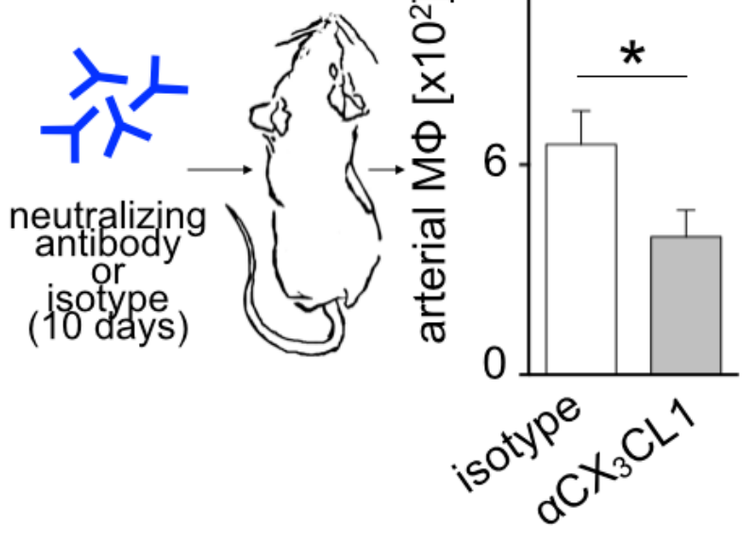
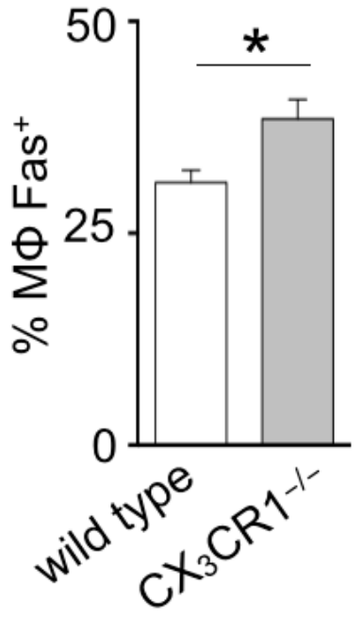
CX_3CL1-CX_3CR1 interactions maintain arterial MΦ survival

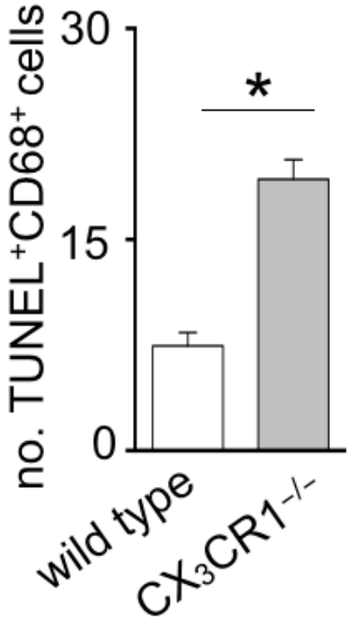




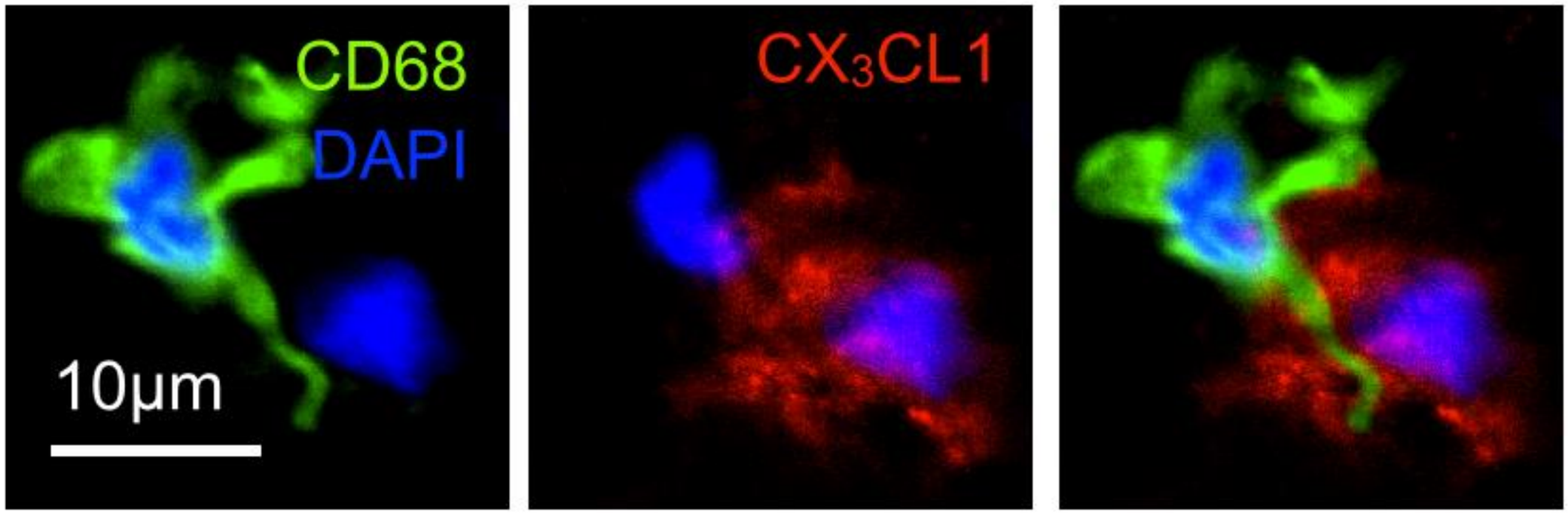








CX_3CL1-CX_3CR1 interactions maintain arterial MΦ survival: The tissue MΦ niche



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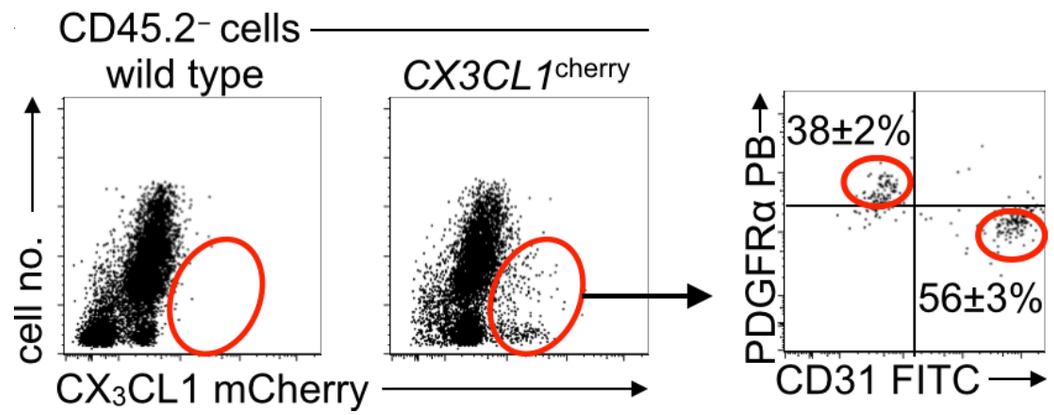
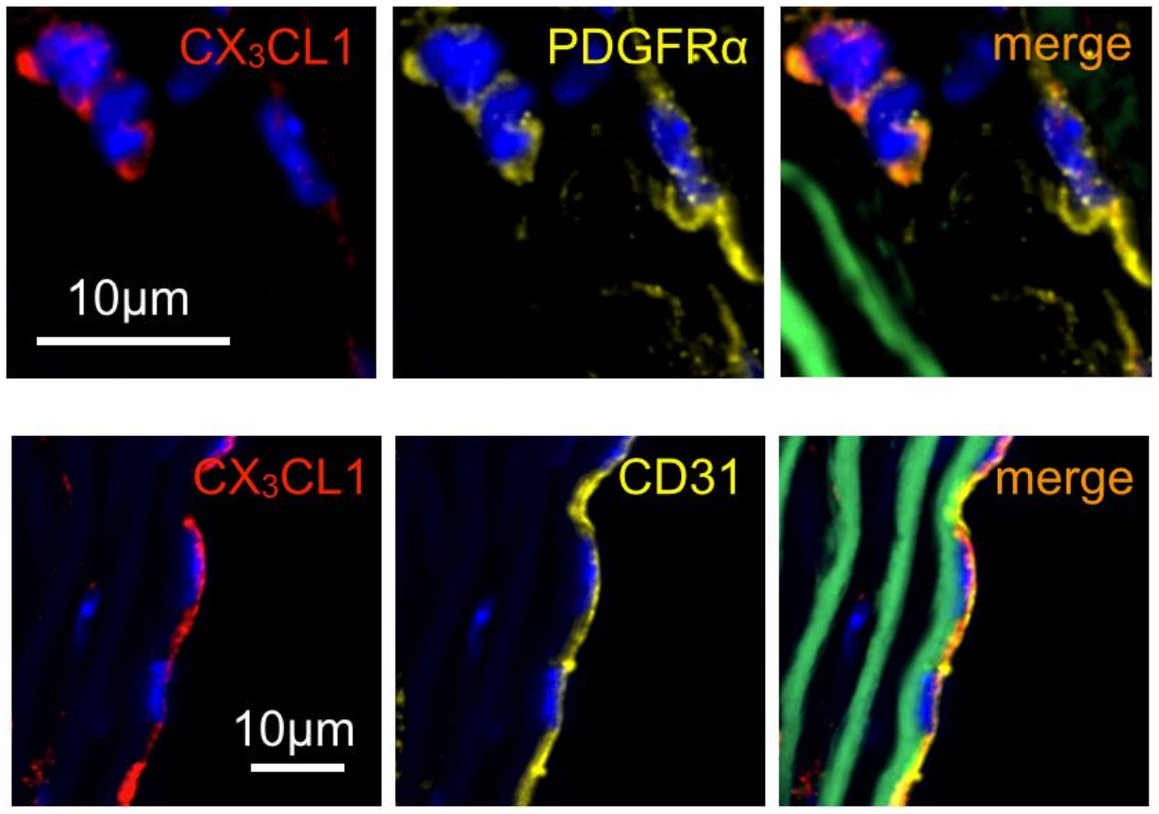
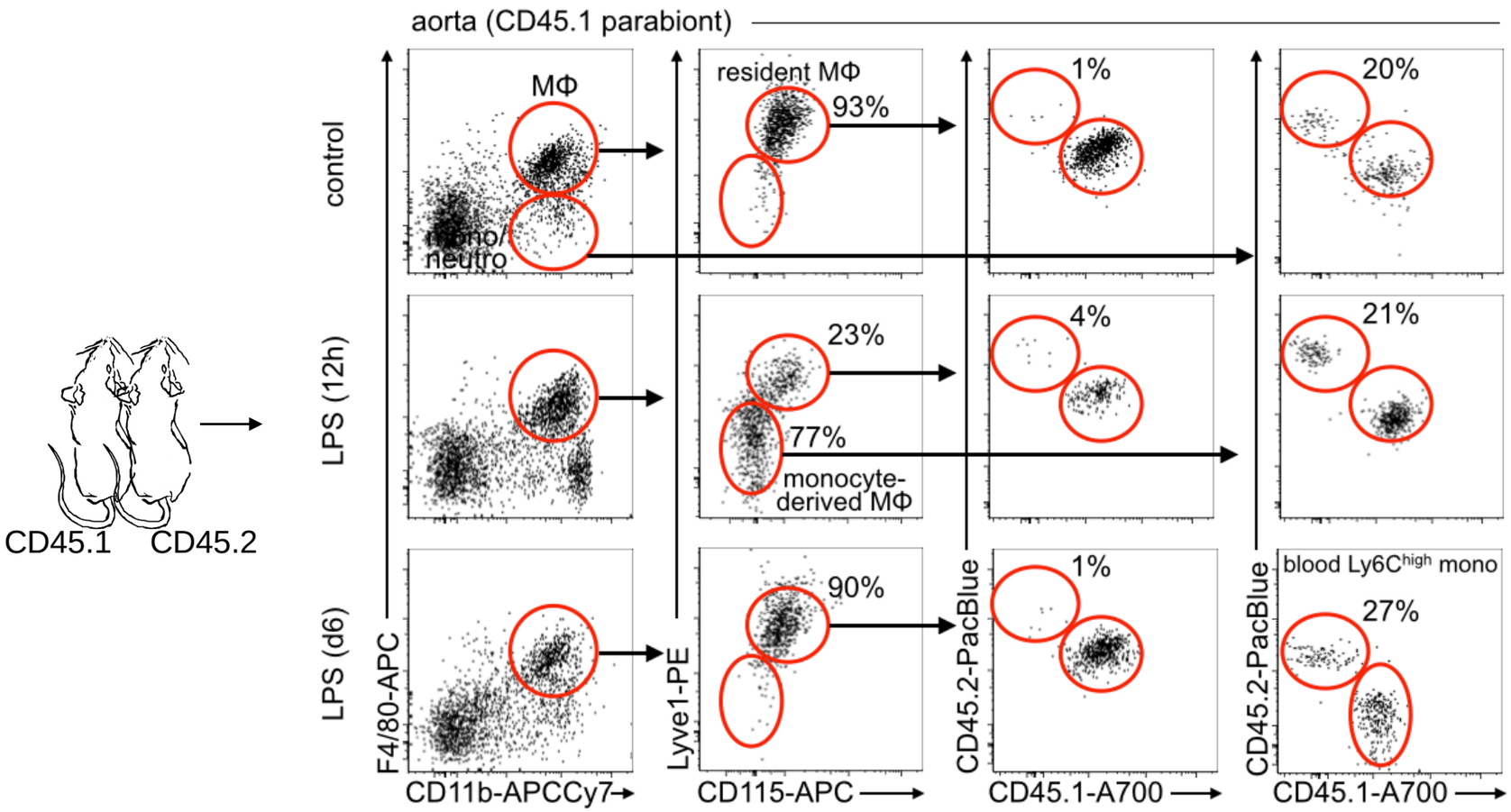
CX_3CL1-CX_3CR1 interactions maintain arterial MΦ survival: arterial MΦ niche





Arterial MΦ responses during inflammation

Arterial macrophage diversity during inflammation



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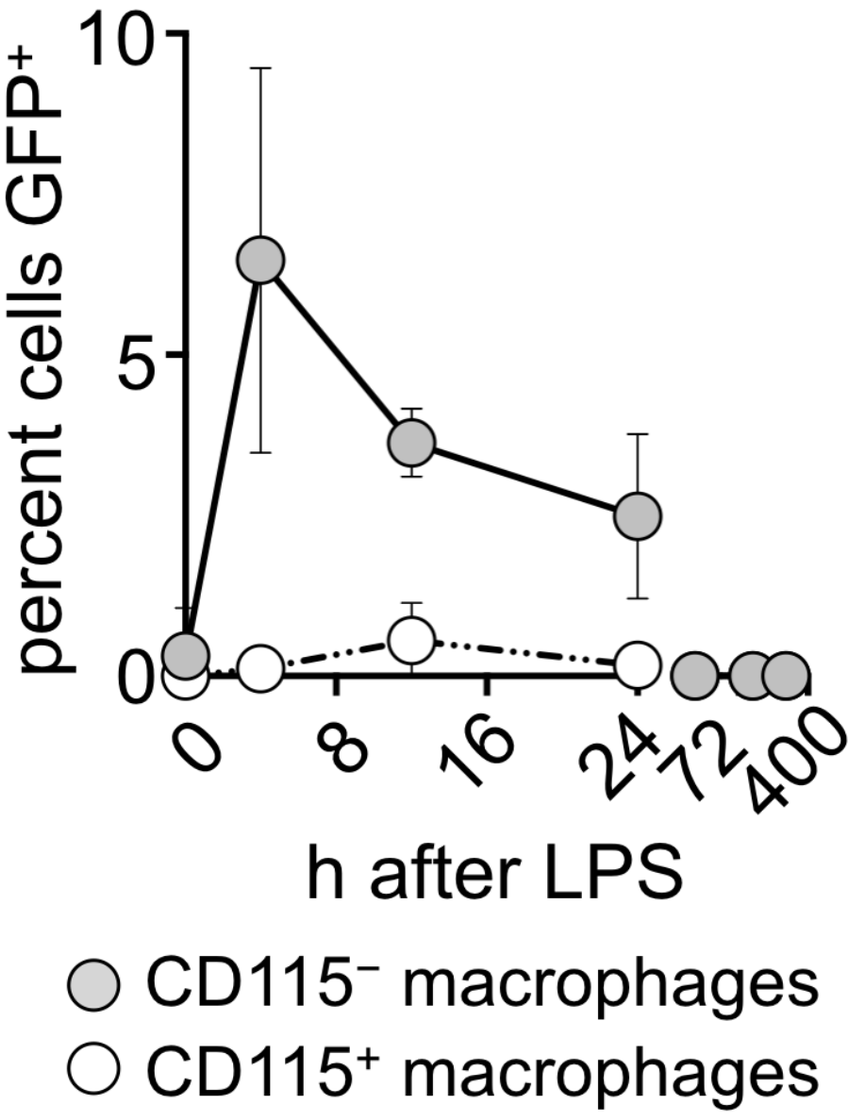
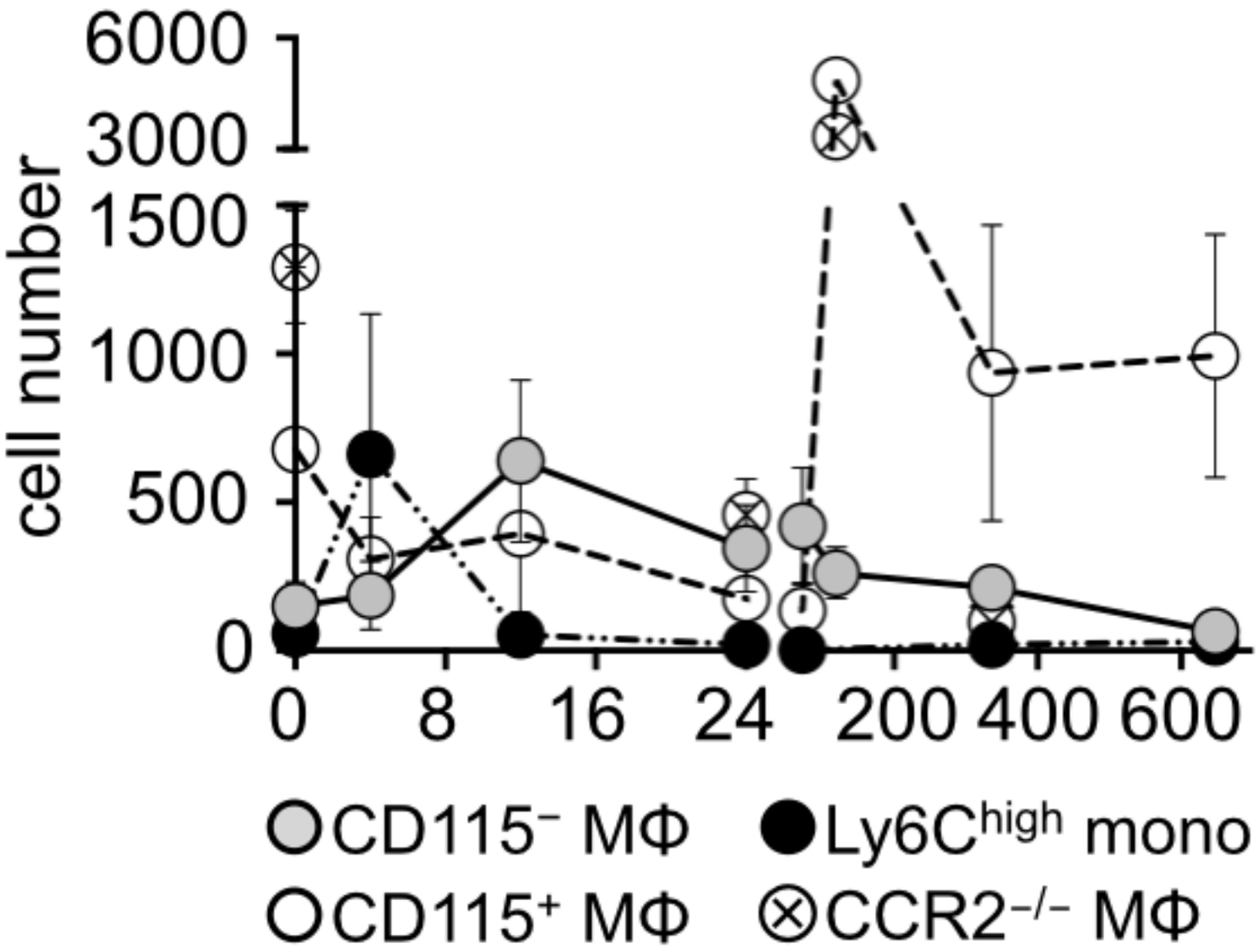
Arterial macrophage diversity during inflammation



Macrophage diversity during inflammation



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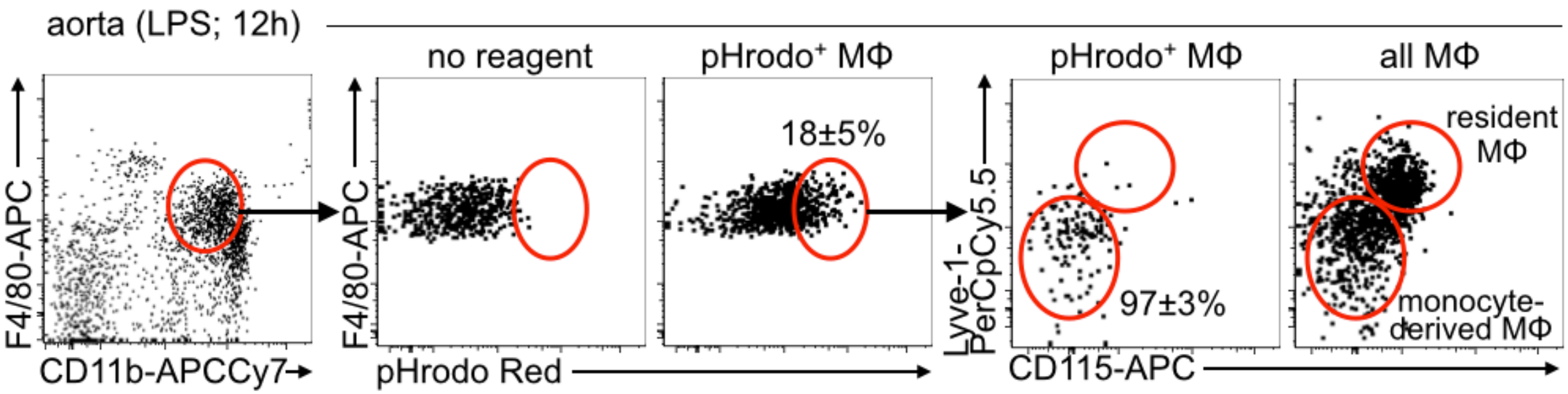
Macrophage diversity during inflammation



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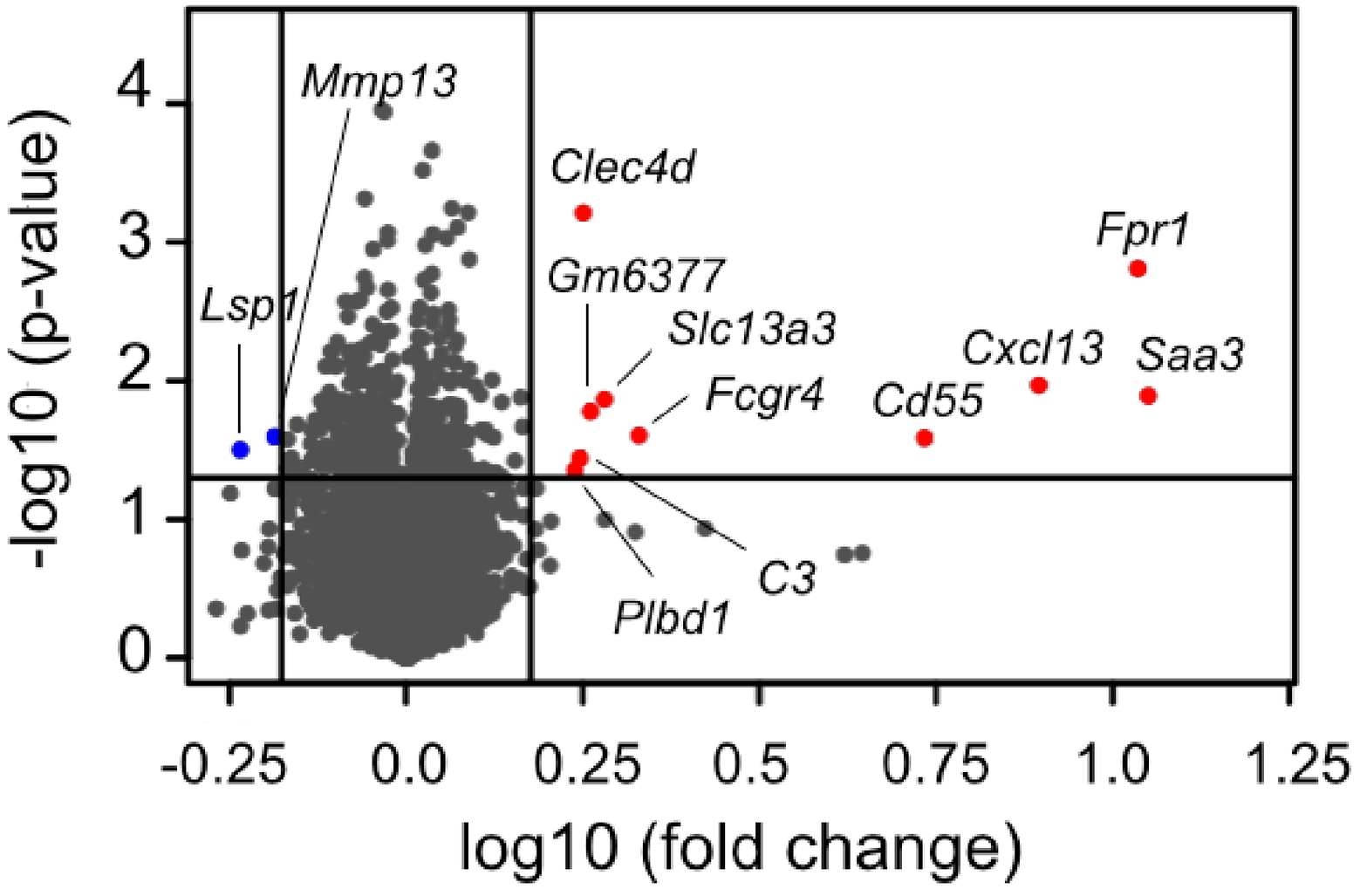
Replenishment of arterial MΦ during inflammation



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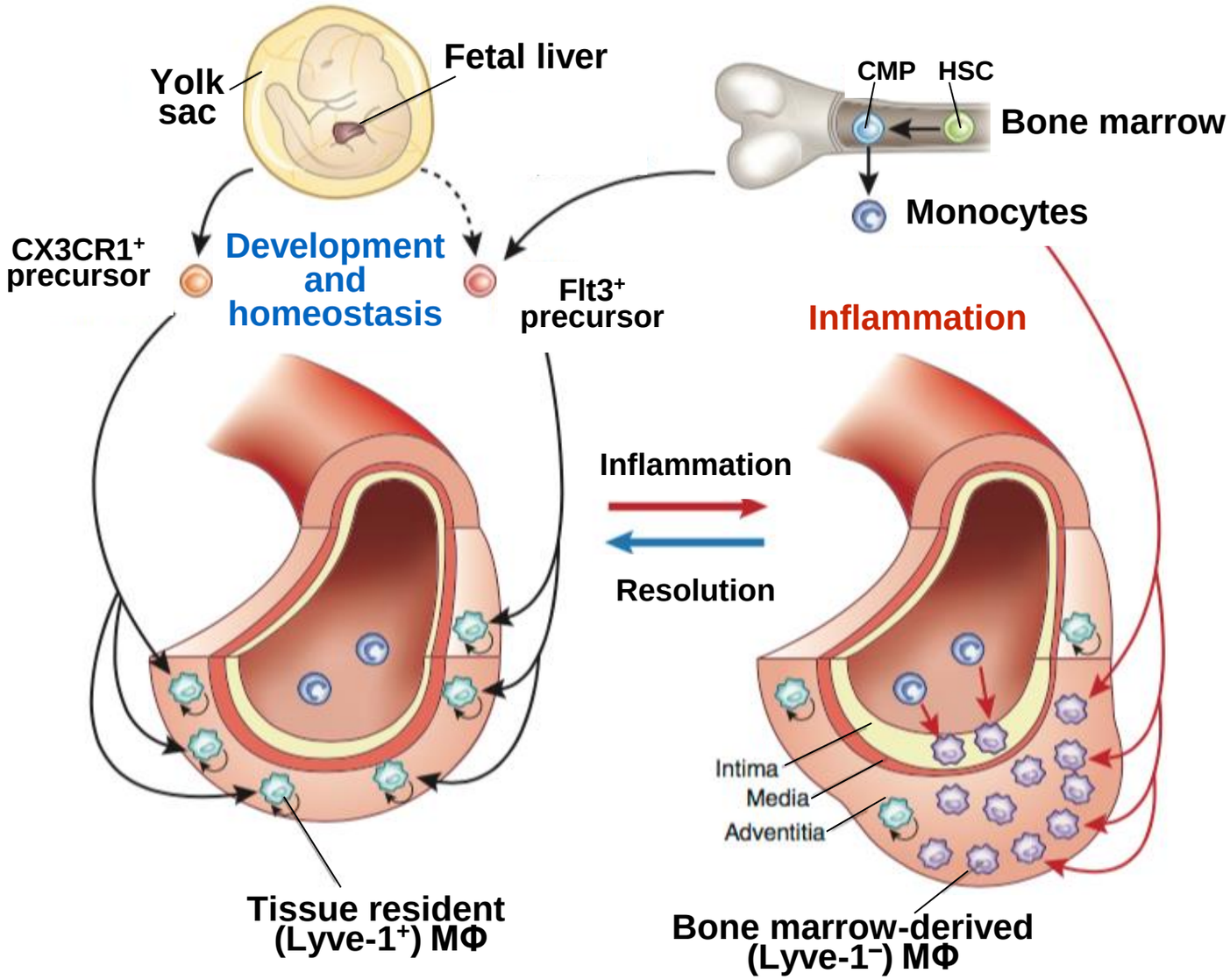
Conclusions



Adapted from Klapproth *et al*. Nature Immunology 2016

- Resident arterial MΦ constitute a distinct population among tissue MΦ.
- Arterial MΦ developmental pathway is unique - arise embryonically from CX_3CR1^+ precursors and postnatally from bone marrow-derived monocytes that colonize the tissue immediately after birth.
- Survival of arterial MΦ within the vascular niche depends on a CX_3CR1/CX_3CL1 axis.
- In adulthood, proliferation sustains arterial MΦ in the steady state and after severe depletion following sepsis.
- After infection, arterial MΦ return to functional homeostasis rapidly.

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