Mitochondria health, cardiac macrophage importance and cardio-myocyte dysfunction

review

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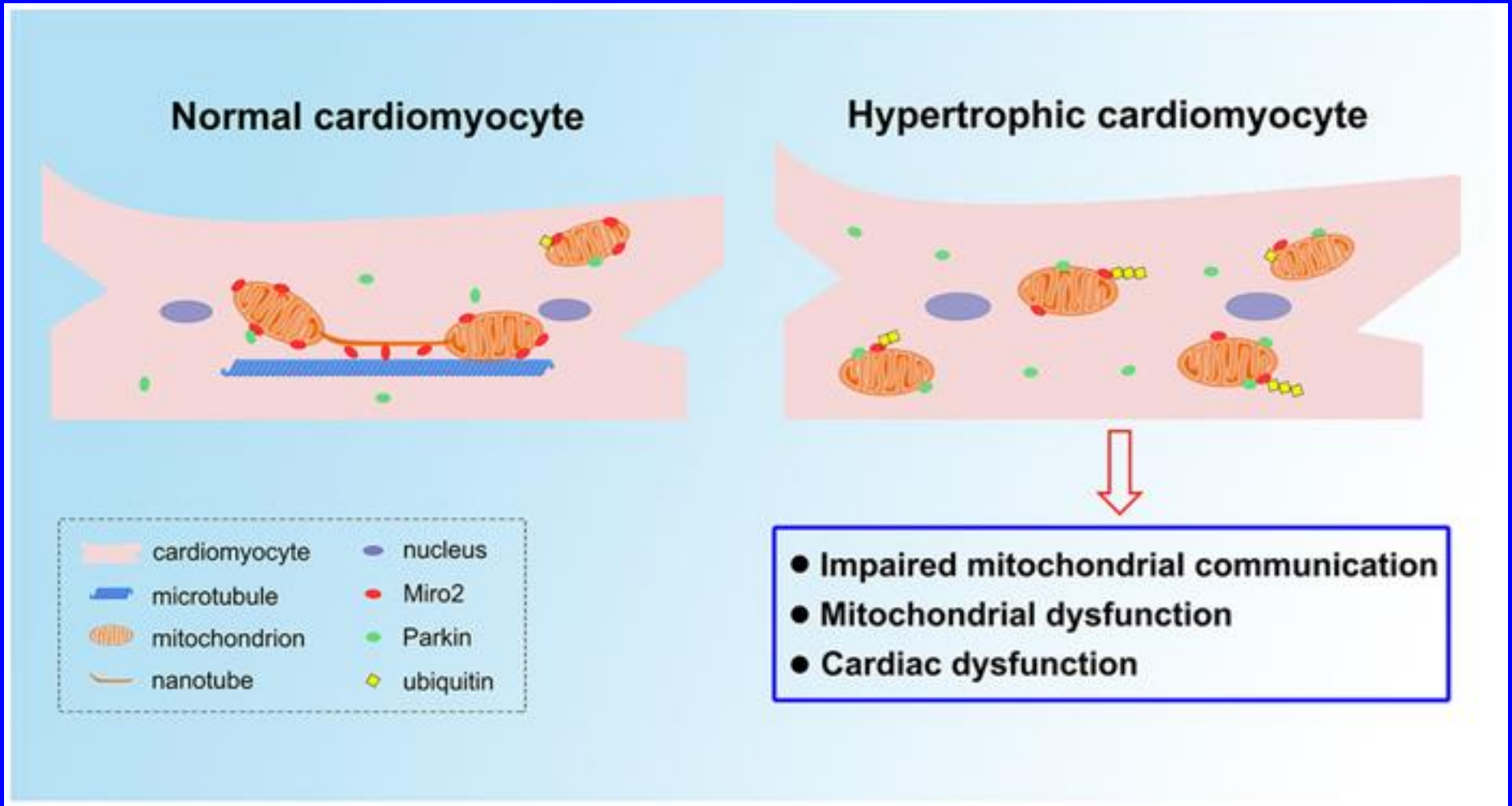
Mitochondria integrity is essential for cardiomyocyte function.
Mitochondrial disfunction and impaired mitochondrial communication are basis for cardiomyocytes disfunction.
Mitochondrial Miro2 expression levels regulate inter-mitochondrial communication along microtubules in adult cardiomyocytes, and degradation of Miro2 through Parkin-mediated ubiquitination contributes to impaired inter-mitochondrial communication and cardiac dysfunction during hypertrophic heart diseases.
Overexpression of Miro2 improves inter-mitochondrial communication and protects cardiac and mitochondrial functions from hypertrophy.
Cardiac tissue macrophages are crucial in monitoring of physiological carciomiocyte state and function. They are important in recognizing stressed carciomiocytes, helping dysfunctional and finally eliminating damaged cardio myocytes by efferocytosis.
They are essentially different both genetically, functionally and by origin from classical, monocyte derived macrophages.
Macs actively phagocytose mitochondrial debris released from cardiac myocytes under physiological conditions, via the receptor tyrosine kinase **Mertk**.
Genetic ablation of cMacs using CD169-driven DTR, or knockout of Mertk, triggers accumulation of mitochondrial debris, impaired autophagy, and NLRP3 inflammasome activation, resulting in compromised heart function and metabolic derangement.
Upon damage or stress activation, glucocorticoid-activated cardiac macrophages promote the active elimination of hypertrophic cardiomyocyte-derived mitochondria and help maintain cardiac health and homeostasis through the induction of the phagocytic receptor **Mer tyrosine kinase** (**Mertk**).

Miro2 Regulates Inter-Mitochondrial Communication in the Heart and Protects Against TAC-Induced Cardiac Dysfunction

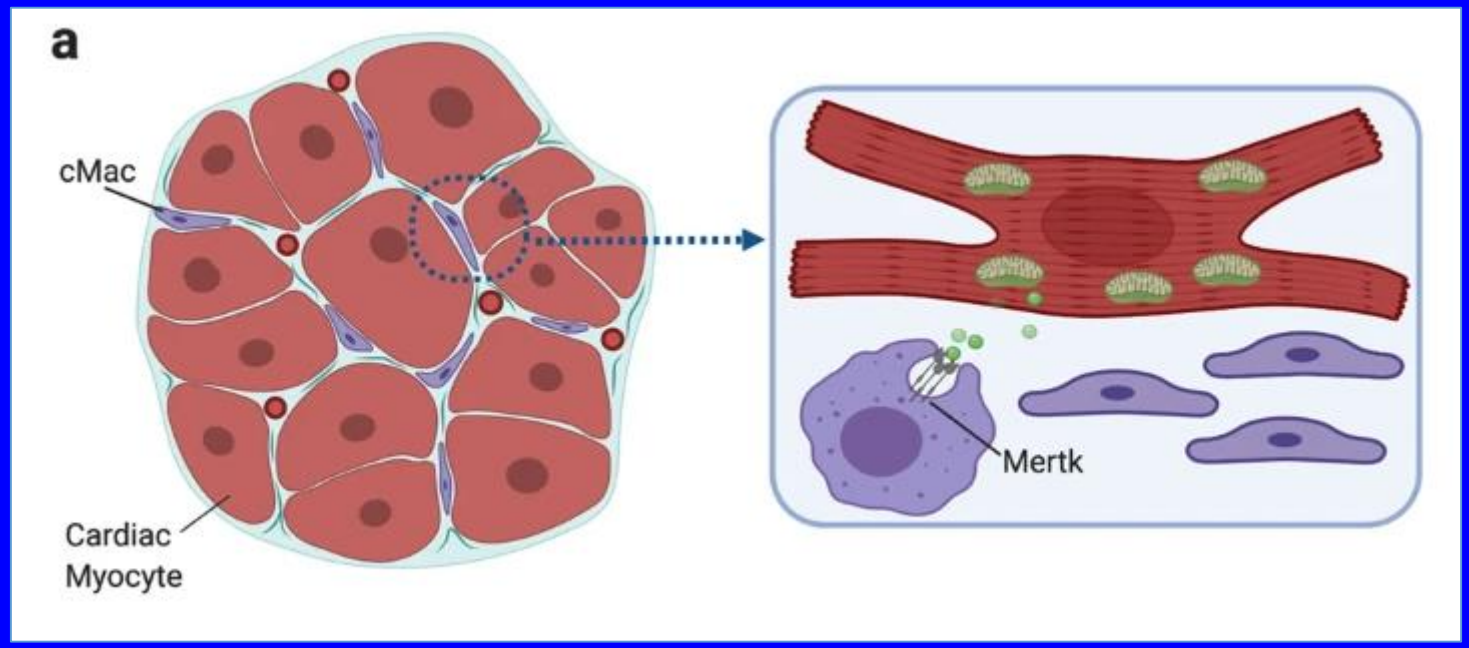


Mitochondrial Miro2 expression levels regulate inter-mitochondrial communication along microtubules in adult cardiomyocytes, and degradation of Miro2 through Parkin-mediated ubiquitination contributes to impaired inter-mitochondrial communication and cardiac dysfunction during hypertrophic heart diseases.

Overexpression of Miro2 improves inter-mitochondrial communication and protects cardiac and mitochondrial functions from hypertrophy.

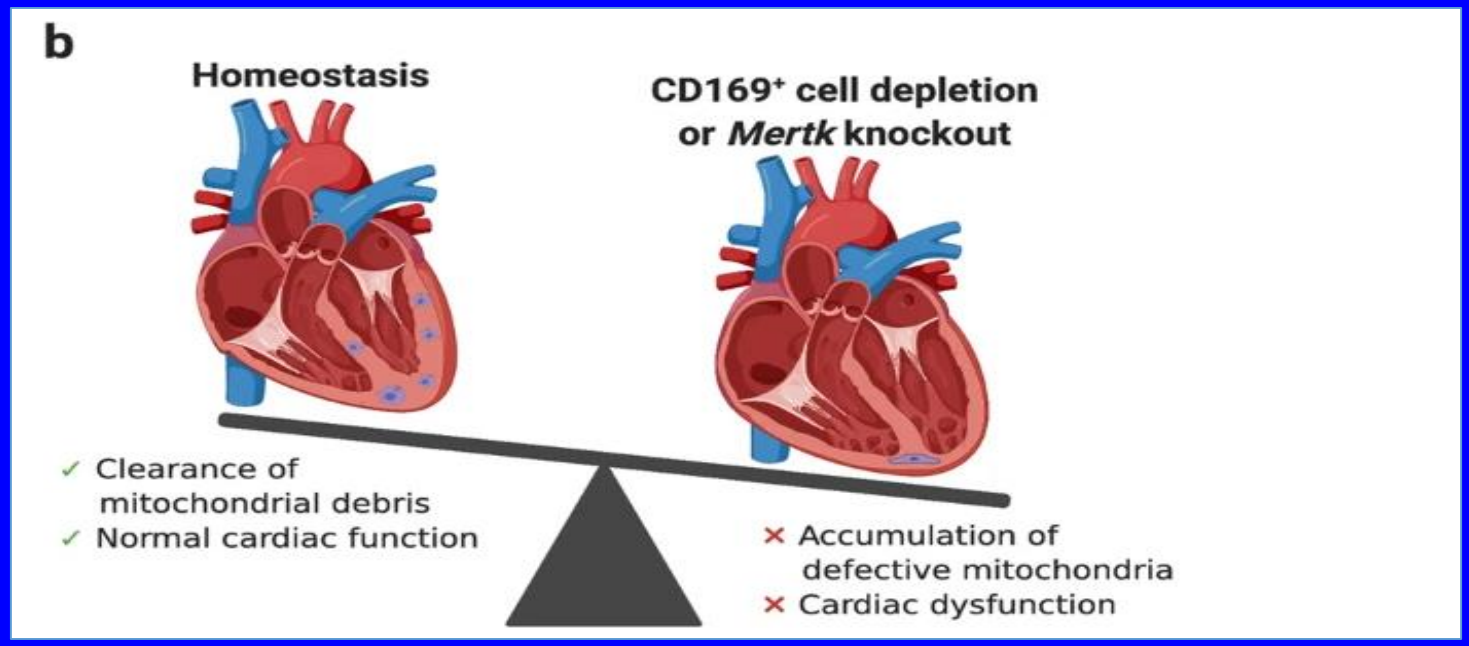
Circulation Research 2019. 125:(8) 728-743, DOI: 10.1161/CIRCRESAHA.119.315432)

Resident macrophages keep mitochondria running in the heart



Cardiac tissue macrophages (cMacs: $CD45^+$ $CD11b^+$ $F4/80^+$ and marked by CX3CR1-GFP) reside in the interstitial compartment of the heart at baseline, with multiple cMacs surrounding each cardiac myocyte.

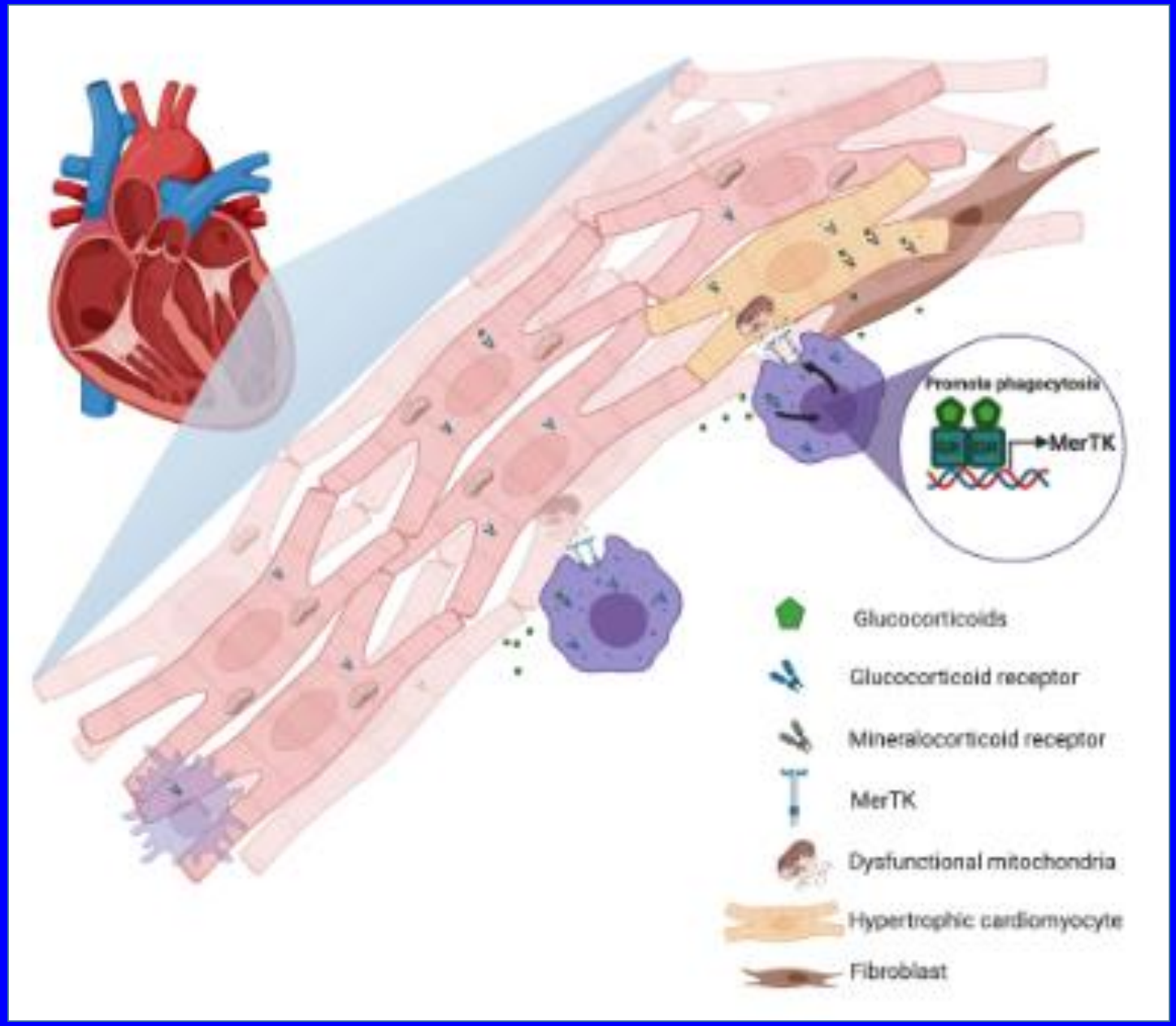
Macs actively phagocytose mitochondrial debris released from cardiac myocytes under physiological conditions, via the receptor tyrosine kinase **Mertk**.



Genetic ablation of cMacs using CD169-driven DTR, or knockout of Mertk, triggers accumulation of mitochondrial debris, impaired autophagy, and NLRP3 inflammasome activation, resulting in compromised heart function and metabolic derangement.

Cell Research (2020) 30:1057–1058; https://doi.org/10.1038/s41422-020-00427-z

Glucocorticoids as Regulators of Macrophage Mediated Tissue Homeostasis



Schematic representation of how glucocorticoids could contribute to cardiac tissue homeostasis.

Upon damage or stress activation, glucocorticoid-activated cardiac macrophages promote the active elimination of hypertrophic cardiomyocyte-derived mitochondria and help maintain cardiac health and homeostasis through the induction of the phagocytic receptor **Mer tyrosine kinase** (**Mertk**).

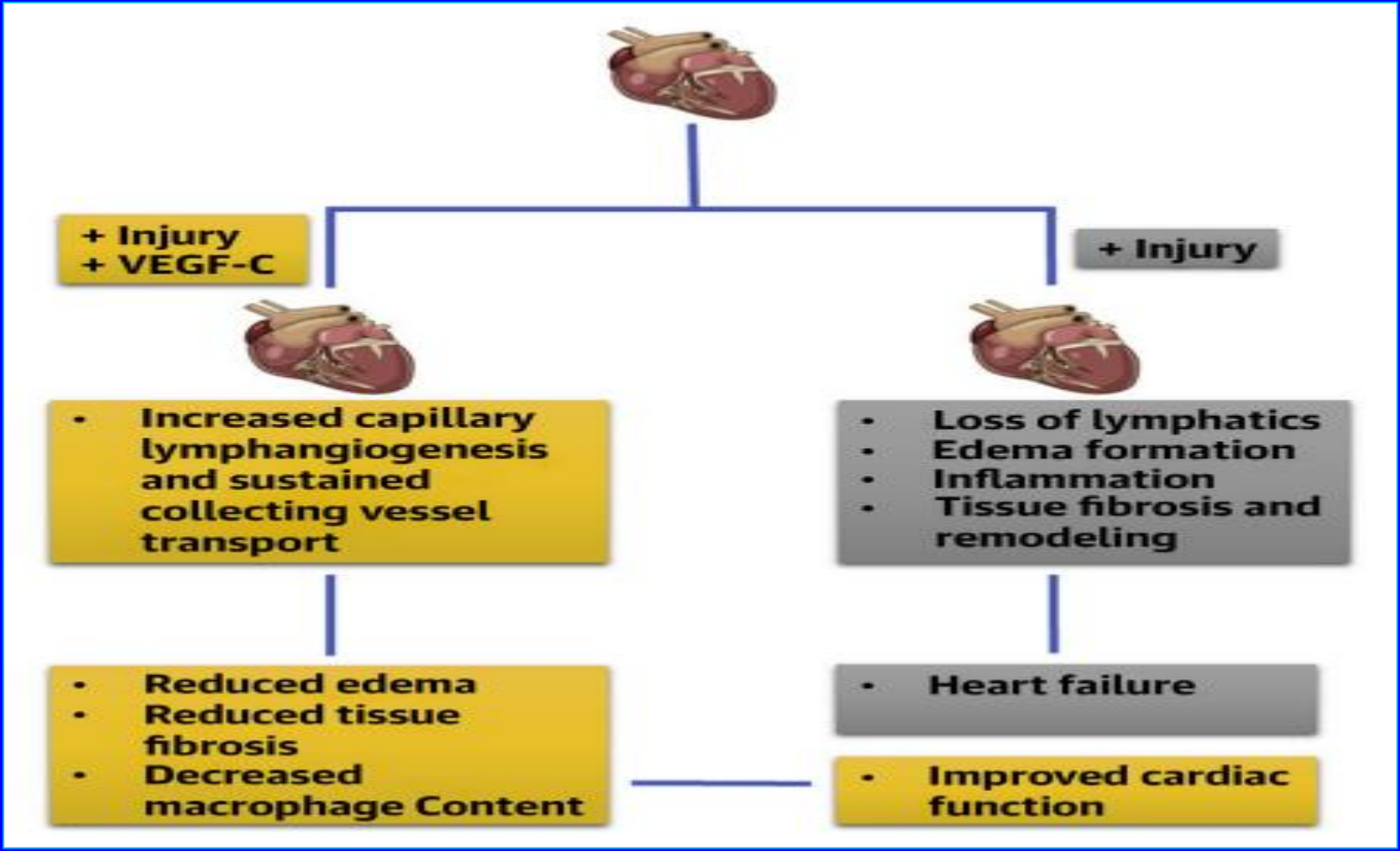
Front. Immunology. 12:669891. DOI: 10.3389/fimmu.2021.669891

Cardiac lymphatic system, heart injury, VEGF-C production of cardiac macrophages and importance of efferocytosis.

Experimental studies demonstrated that Miocardial Infarct - induced robust, intra myocardial capillary lymph-angiogenesis, adverse remodeling of epicardia pre-collector and collector lymphatics occurred, leading to reduced cardiac lymphatic transport capacity.
Consequently, myocardial edema persisted for several months post-MI, extending from the infarct to non-infarcted myocardium. Intra myocardial-targeted delivery of the vascular endothelial growth factor receptor 3-selective designer protein **VEGF-C**C152S, using albumin-alginate micro particles, accelerated cardiac lymph-angiogenesis in a dose-dependent manner and limited pre-collector remodeling post-MI.
As a result, myocardial fluid balance was improved, and cardiac inflammation, fibrosis, and dysfunction were attenuated.
Circulation 2016;133(15):1484-97; doi: 10.1161/CIRCULATIONAHA.115.020143
J Am Coll Cardiol Basic Trans Science. 2017;2(4):477–83.

The immune response to ischemic myocardial injury mobilizes innate and adaptive immune cells to the site of injury. Efferocytosis is one mechanism by which myocardial MF coordinate cardiac repair by simultaneously clearing cell debris, taking up cardiac antigens, and trafficking to the lymph nodes where MF enhance the adaptive immune response necessary for myocardial healing. These steps position the immune response and the lymphatic system at the epicenter of cardiac repair. While the role of cardiac lymphatics has been extensively studied during cardiac development, its role in cardiac repair is only recently emerging. Since defective efferocytosis leads to accelerated HF in mice, understanding the crosstalk between efferocytosis and lymphatics is an exciting avenue of investigation that may provide insight into the pathogenic processes underlying chronic ischemic HF. Efferocytosis triggers myeloid VEGFC production, which, in turn, promotes the lymphangiogenic response in cardiac repair, thus positioning myeloid-derived VEGFC in the midst of the complex interplay between the inflammatory and lymphangiogenic responses to myocardial ischemia. This myeloid VEGFC production is CD36 mediated.
J Clin Invest. 2022;132(9):e140685. https://doi.org/10.1172/JCI140685.
J Clin Invest DOI: 10.1172/JCI158703.

VEGF-C Treatment After Injury Promotes Heart Function

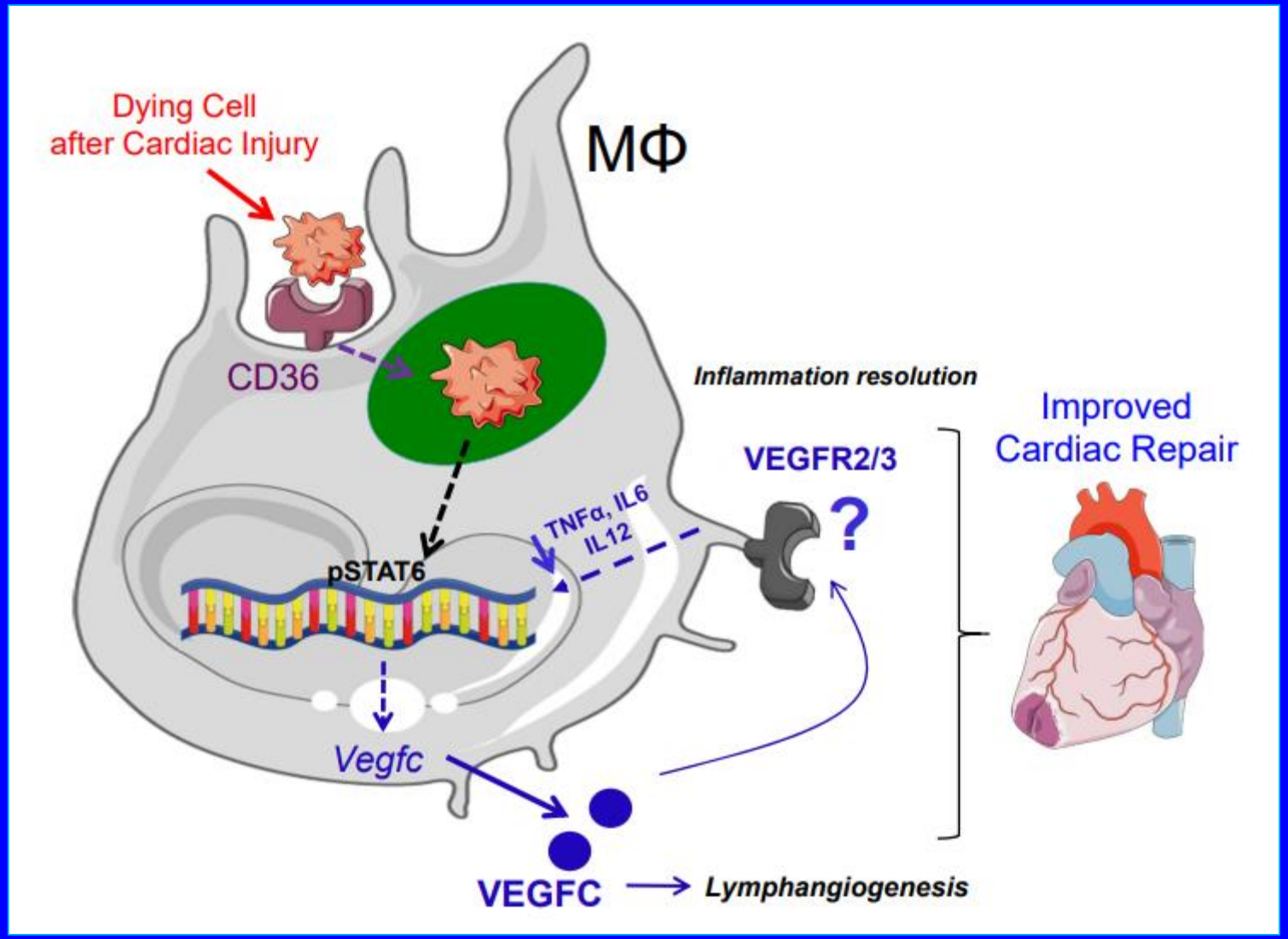


Although it has been appreciated that the heart relies on lymphatic vessels to maintain fluid balance and that such balance must be tightly maintained to allow for normal cardiac output, it has only recently come to light that the lymphatic vasculature may serve as a therapeutic target with which to promote optimal healing following myocardial ischemia and infarction. Key role in maintaining lymphatic vessels after ischemic heart lession belong to VEGF-C.

Given the role of VEGF-C in wound repair to induce lymph-angiogenesis, its use therapeutically benefits lymphedema. To investigate the influence of lymph-angiogenesis on cardiac function, VEGF-C therapy was applied after myocardial infarction and found to improve cardiac function post-myocardial infarction while limiting fibrosis and lingering inflammation

Huang, L.-H. et al. J Am Coll Cardiol Basic Trans Science. 2017;2(4):477–83.

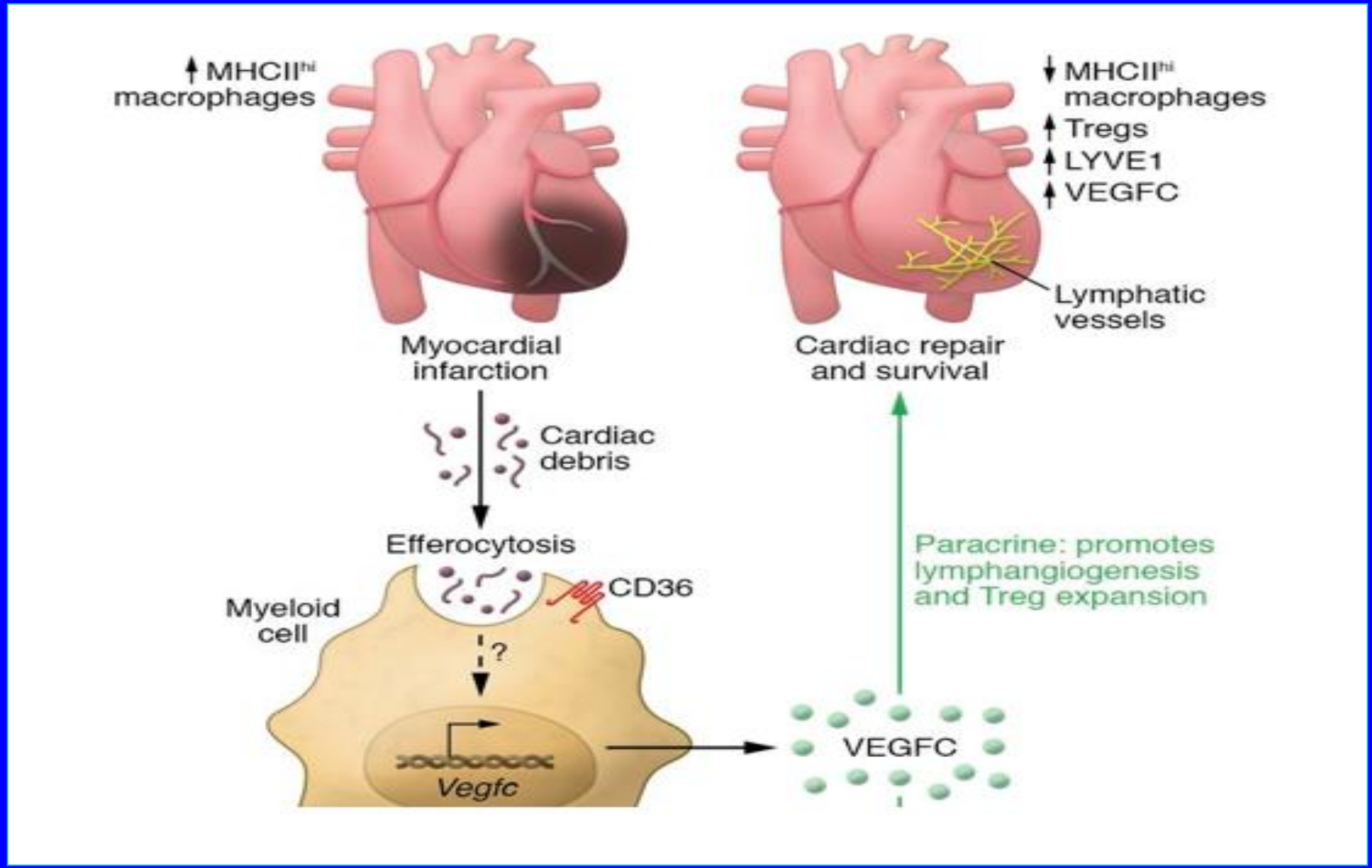
Macrophage-produced VEGFC is induced by efferocytosis to ameliorate cardiac injury and inflammation



Myeloid cells produced VEGF-C after cardiac injury exerts cardio-protective role.
We also report that efferocytosis, as occurs after tissue injury, is a trigger for *Vegfc* induction.

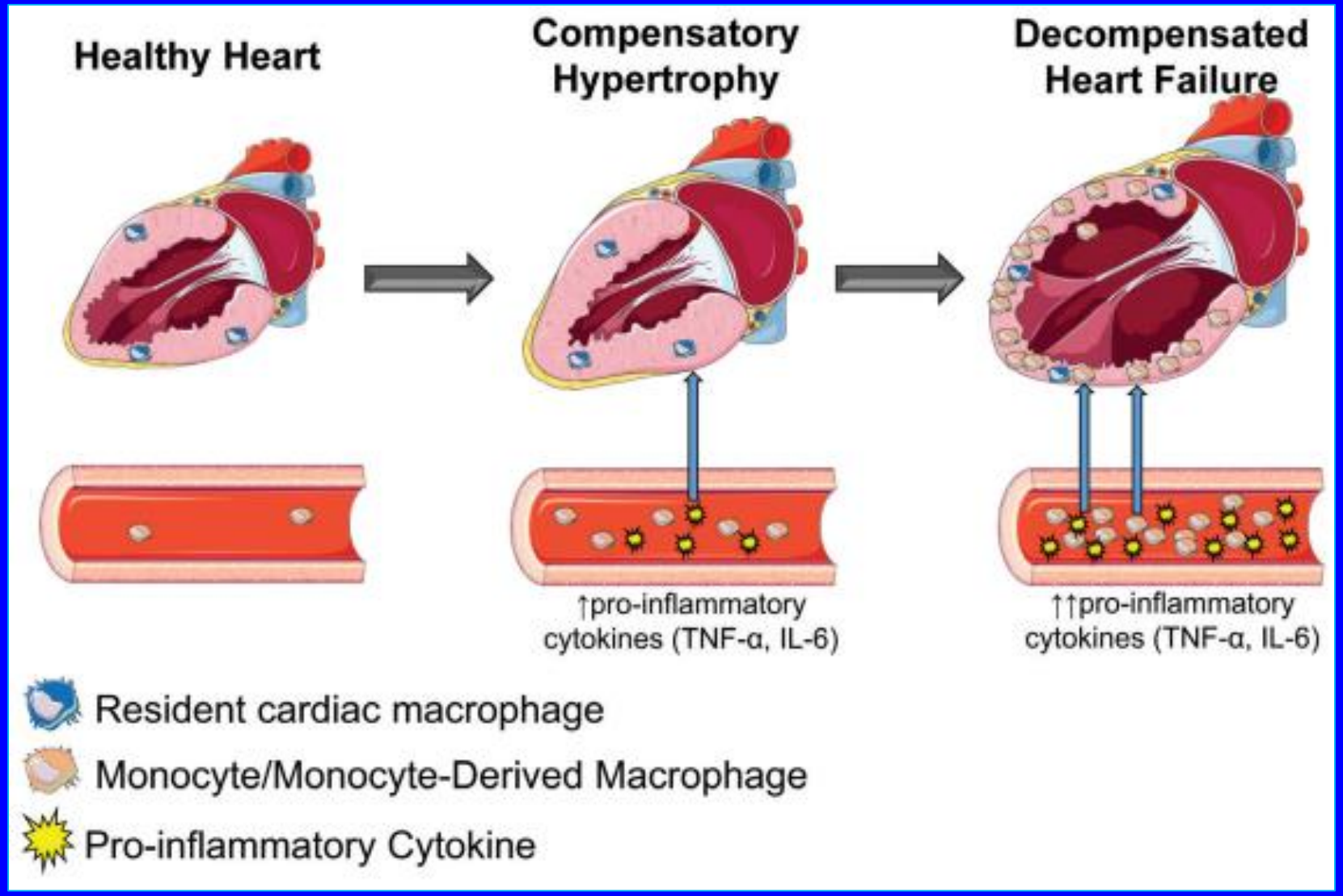
J Clin Invest. 2022;132(9):e140685. https://doi.org/10.1172/JCI140685.

Macrophage efferocytosis with VEGFC and lymphangiogenesis: rescuing the broken heart



J Clin Invest DOI: 10.1172/JCI158703

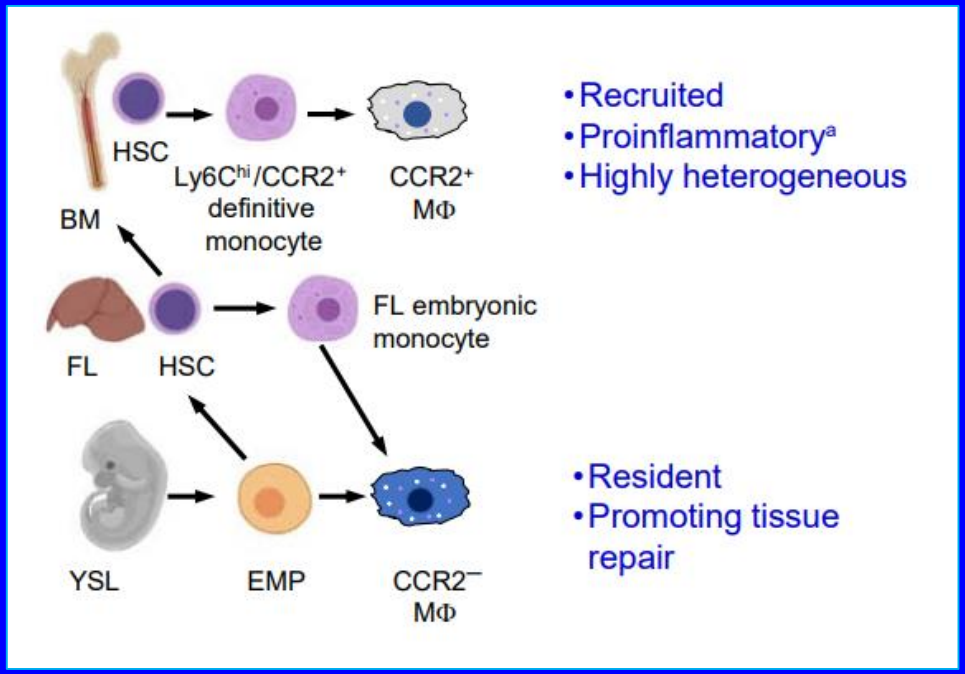
Role of macrophages and inflammation during the transition to decompensated heart failure



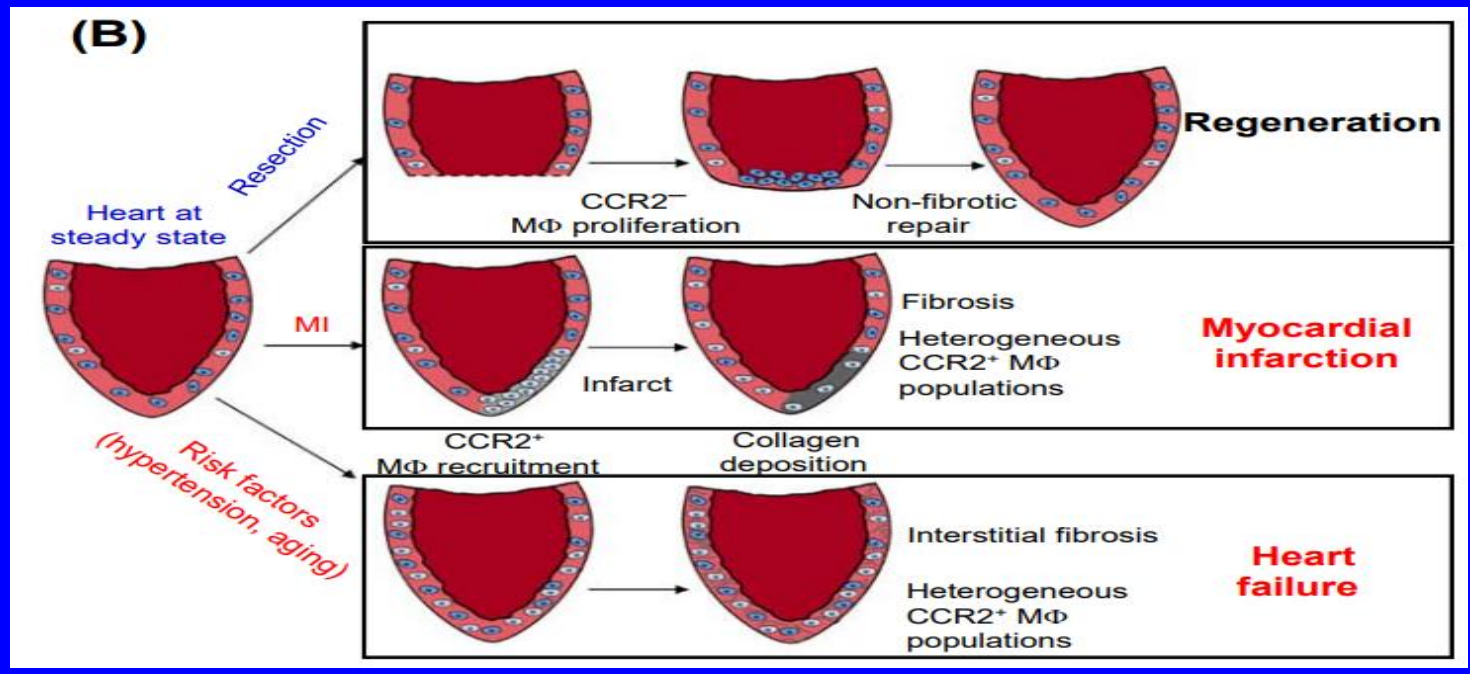
In healthy individuals, the heart is populated sparsely with quiescent resident macrophages (blue). During compensatory hypertrophy, there are increased circulating pro inflammatory monocytes and cytokines but no changes in cardiac macrophage numbers. When decompensation occurs, circulating levels of pro inflammatory monocytes and cytokines are further increased, and circulating monocytes begin infiltrating the injured heart.

Circulation Research. 2020;126:789–806. DOI: 10.1161/CIRCRESAHA.119.312321

Origin and Function of Cardiac Macrophages in Mice and Humans



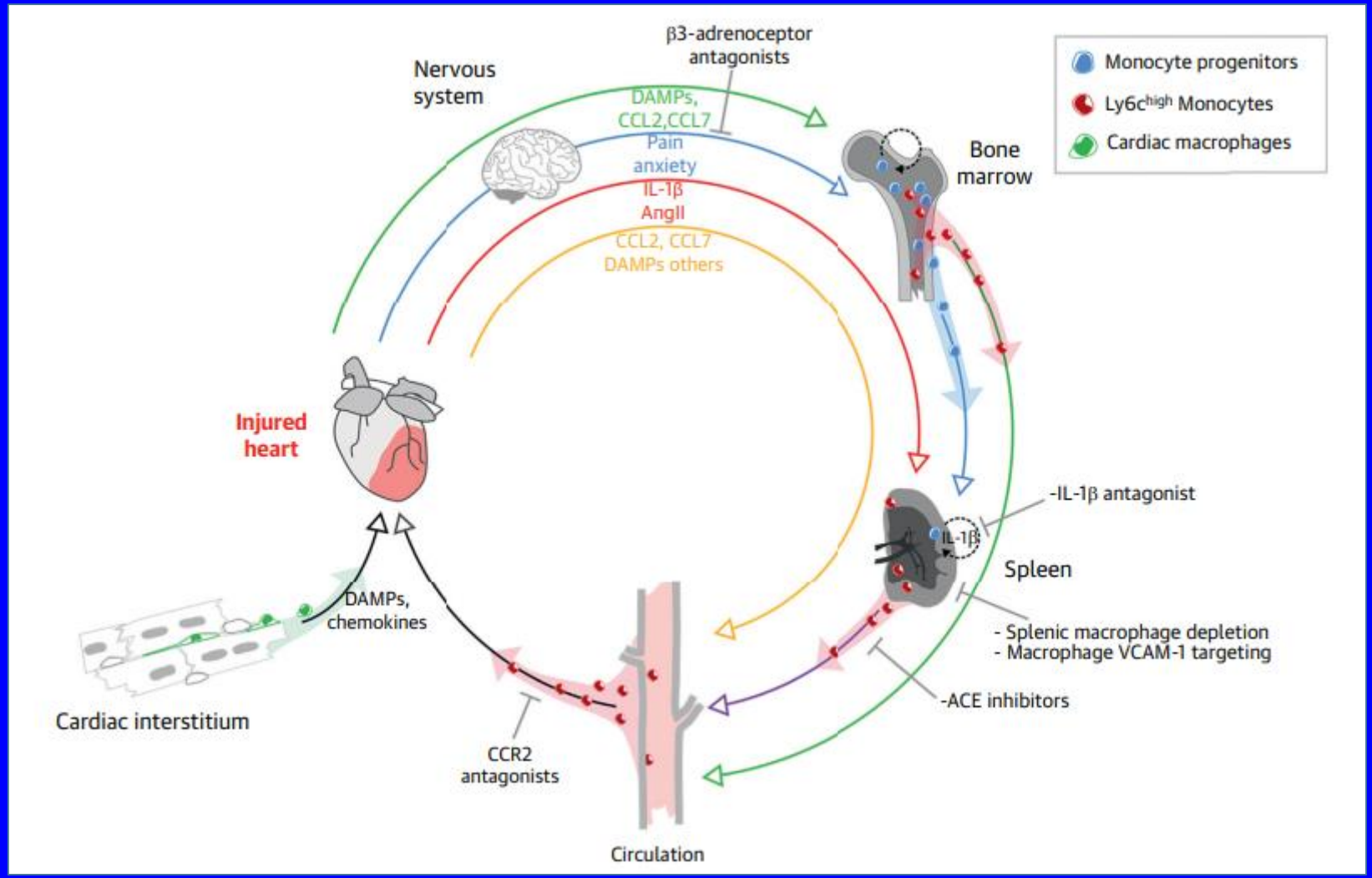
CCR2+ MF are derived from recruited Ly6Chi/CCR2+ monocytes that develop from definitive hematopoietic stem cells (HSCs) with origins in the fetal liver (FL) and bone marrow (BM). CCR2− MF differentiate from erythromyeloid progenitors (EMPs) that are specified in the yolk sac as well as HSCs from the FL. FL Mo, which are derived from a population of yolk syncytial layer (YSL) EMPs, remain a poorly understood population.



Models of MF roles in heart regeneration and disease are shown. In hearts with regenerative capacity, such as neonatal mice and lower vertebrates, injury/resection results in local proliferation of CCR2− MF at the site of injury, promoting non-fibrotic repair. Following myocardial infarction (MI) in adult murine hearts without regenerative capacity, resident CCR2− MF die and Mo derived MF, which retain CCR2 expression, are recruited to the infarct where they promote inflammation and stimulate collagen deposition, resulting in localized fibrosis at the site of injury. In the case of heart failure, CCR2− MF are recruited to the failing heart but are not localized to a single site, resulting in the formation of interstitial fibrosis that stiffens the ventricular wall, decreasing cardiac function. Radiolabeled probes have also demonstrated that CCR2+ cells are recruited to acute MI sites and failing hearts in humans. a Although recruited Mo-derived MF represent predominantly pro inflammatory MF, a smaller population of recruited MF demonstrate wound-healing properties, in contrast to the majority of the recruited population.

Trends in Immunology, 2019, 40(9), 827-841, https://doi.org/10.1016/j.it.2019.07.002

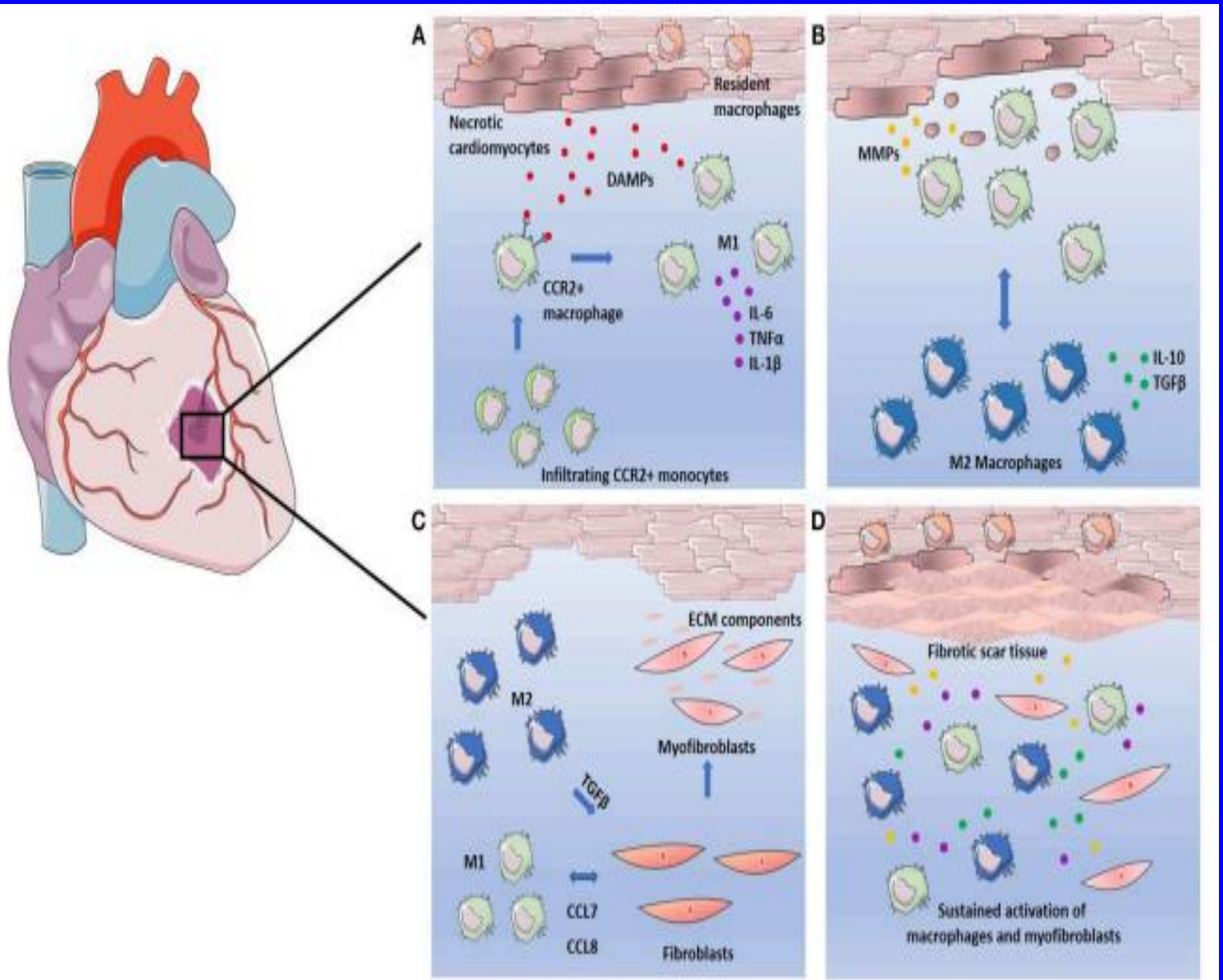
Signaling Circuitry Promoting Monocyte and Macrophage Accumulation in the Injured Heart



(Green pathway) Circulating DAMPs and inflammatory mediators mobilize bone marrow hematopoietic progenitors and monocytes. Monocytes enter the circulation, whereas progenitors migrate to the spleen and support splenic mono-cytopoesis. Monocytes from the bone marrow and spleen eventually arrive at the injured heart. (Blue pathway) Pain and anxiety activate sympathetic pathways suppressing hematopoietic progenitor retention factors in the bone marrow leading to further progenitor cell release. (Red pathway) The injured heart directly signals to the spleen and induces splenic mono-cytopoesis and hematopoietic progenitor cell proliferation by IL-1β – and Ang II-dependent mechanisms. (Yellow pathway) Inflammatory mediators and DAMPs signal directly to recruit monocytes. Adapted from Libby et al.

J Am Coll Cardiol 2018;72:2213–30. https://doi.org/10.1016/j.jacc.2018.08.2149

The Role of Macrophages in the Infarcted Myocardium: Orchestrators of ECM Remodeling



Macrophages in the response to infarction.

(A) Cardiomyocytes undergo necrosis, releasing DAMPs and attracting CCR2+ circulating monocytes. CCR2+ monocytes differentiate into pro-inflammatory M1 macrophages replacing resident macrophages and secreting high levels of pro-inflammatory cytokines IL-6, TNFα, and IL-1β.

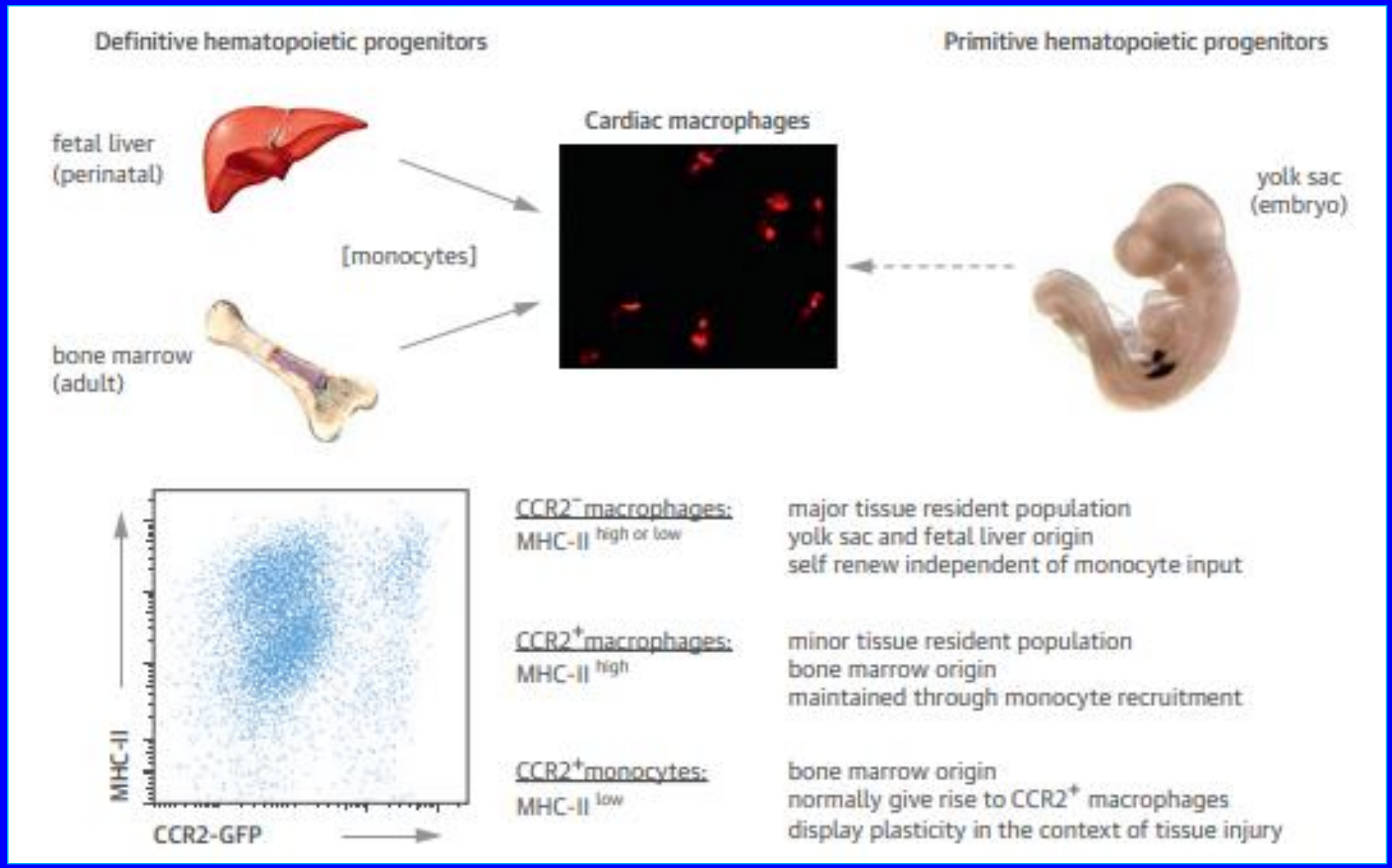
(B) M1 macrophages clear necrotic cell debris through phagocytosis and induce breakdown of the ECM through secretion of MMPs. Phagocytosis of the necrotic debris causes macrophage polarization to the M2 phenotype. M2 macrophages secrete high levels of anti-inflammatory cytokine IL-10 and growth factor TGFβ.

(C) Both M1 and M2 macrophages facilitate the fibrotic response. M1 macrophages recruit fibroblasts via CCL7 and CCL8 mediated signaling. M2 macrophages induce fibroblast differentiation into myofibroblasts, which in turn secrete ECM components to facilitate tissue repair.

(D) Sustained activation of macrophages leads to continuous secretion of growth factors, pro-inflammatory cytokines, and MMPs. Continued breakdown of ECM as well as overproduction of ECM components by myofibroblasts leads to adverse remodeling of ECM and results in fibrotic scar tissue.

Front. Cardiovasc. Med. 6:101. DOI: 10.3389/fcvm.2019.00101

Macrophage Heterogeneity and Functions in the Adult Mouse Heart

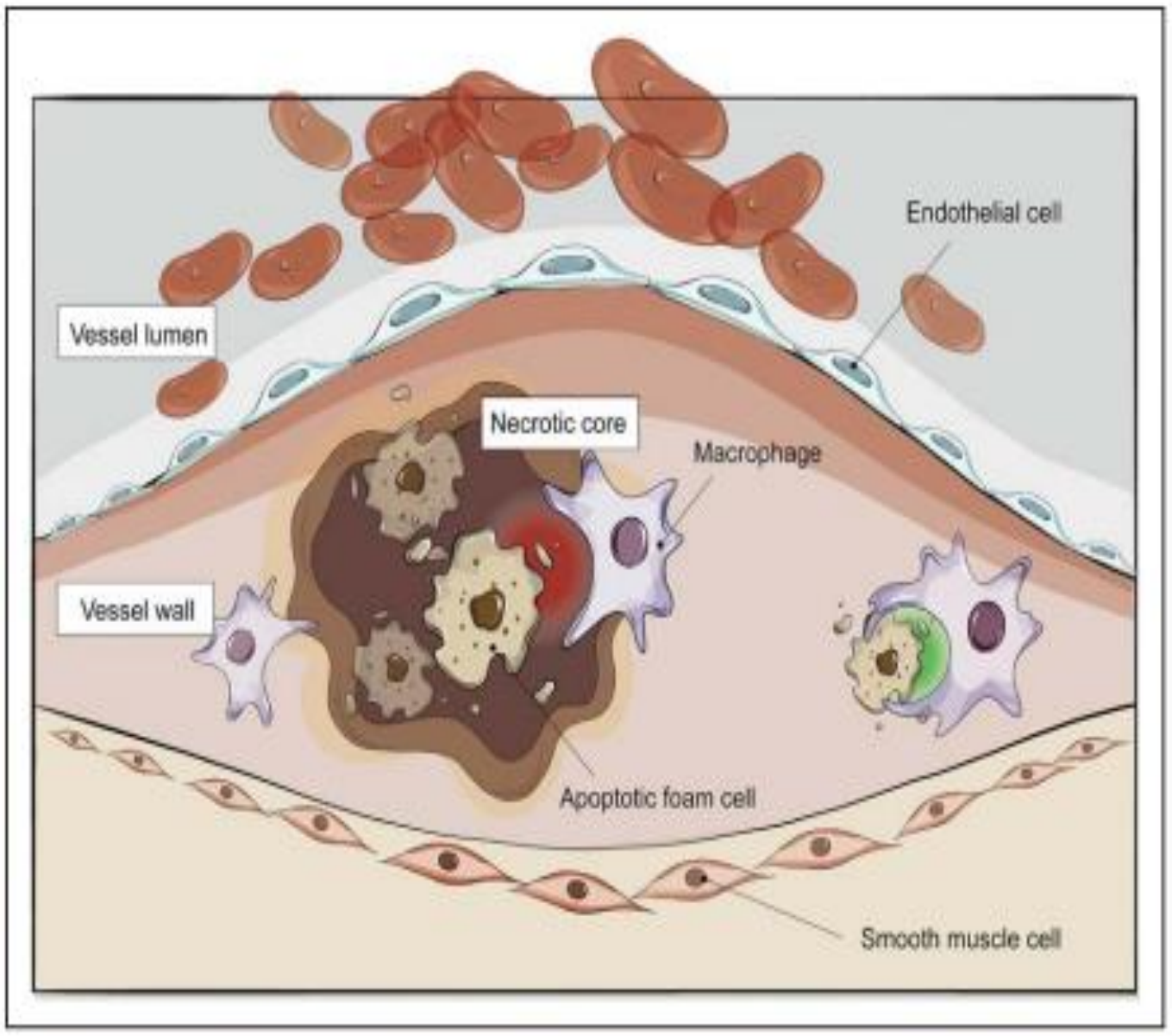


(Top) Schematic depicting the developmental origins of cardiac macrophages.

(Bottom) Flow cytometry showing MF populations within the adult heart during homeostasis and the mechanisms by which each population is maintained. CCR2 expression was examined by measuring GFP fluorescence in Ccr2-GFP reporter mice. Adapted from Lavine et al.

J Am Coll Cardiol 2018;72:2213–30. https://doi.org/10.1016/j.jacc.2018.08.2149

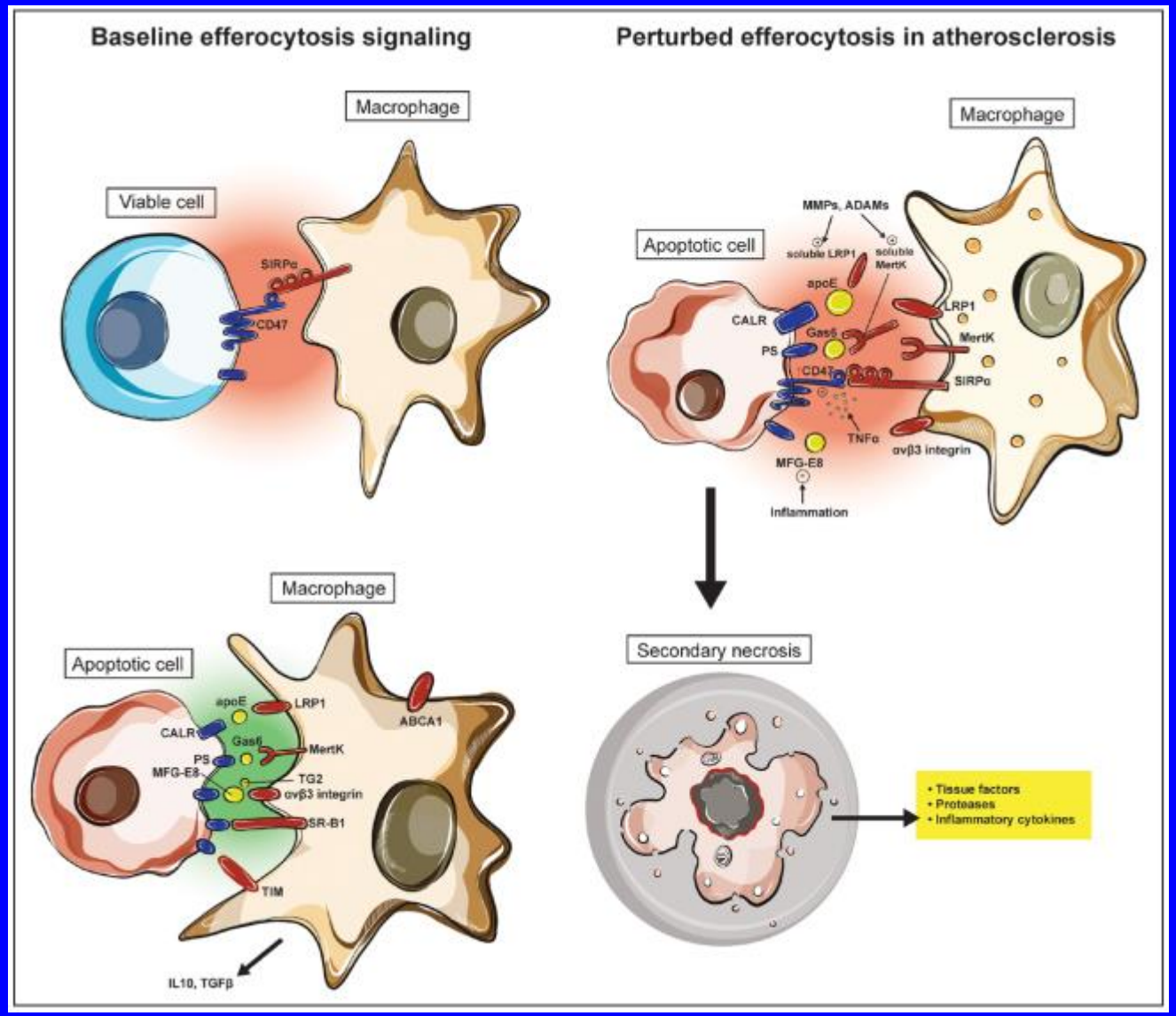
The Role of Efferocytosis in Atherosclerosis



Impaired efferocytosis contributes to atherosclerosis. Diseased and apoptotic cells in the growing atherosclerotic plaque are not recognized for efficient phagocytic clearance by lesional macrophages. Although the mechanisms that drive this pathology are still an area of active investigation, emerging data suggest that this defect may be due to impaired eat me (green) and don't eat me (red) signaling that renders these cells inedible. As a result, foam cells accumulate to promote lesion expansion, and apoptotic tissue undergoes secondary necrosis to accelerate vascular inflammation and lesion instability.

Circulation. 2017;135:476–489. DOI: 10.1161/CIRCULATIONAHA.116.025684

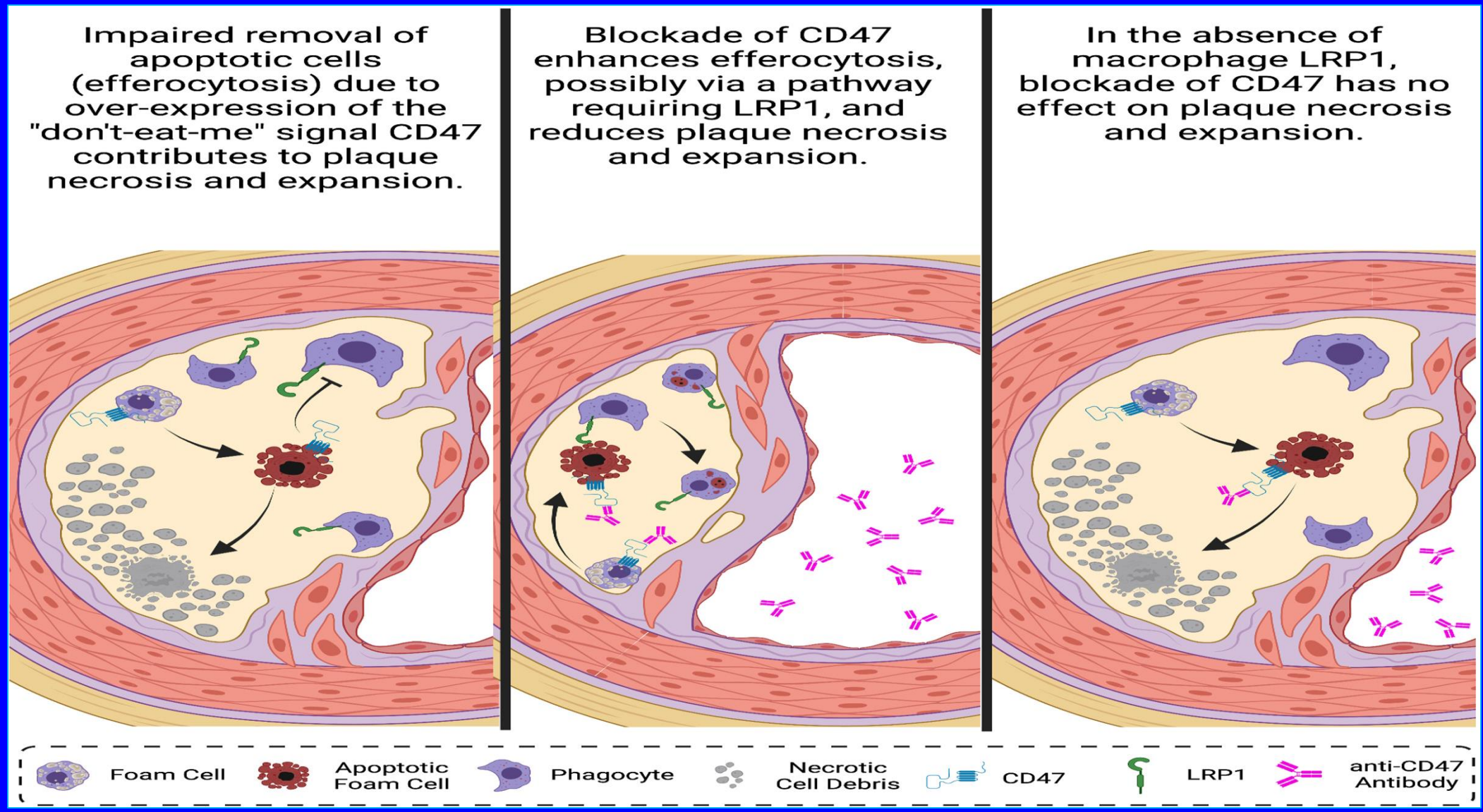
The Role of Efferocytosis in Atherosclerosis



Impaired efferocytosis signaling in vascular disease. Experimental data suggest that prophagocytic signals (including calreticulin, milk fat globule-epidermal growth factor factor 8 [Mfg-e8], and **Mer receptor tyrosine kinase** [**Mertk**]) are reduced in atherosclerosis caused by inflammation, posttranslational modifications, and genetic variability. Exacerbating this loss of eat me signaling is a concomitant upregulation of the CD47-signal regulatory protein alpha don't eat me pathway, which furthers decreases the edibility of cells within the necrotic core. The end result is that apoptotic cells in the growing plaque becomes poor substrates for phagocytic cells, such as macrophages and dendritic cells. Such uncleared cells become secondarily necrotic and release additional pro inflammatory stimuli, thus promoting a positive feedback loop.

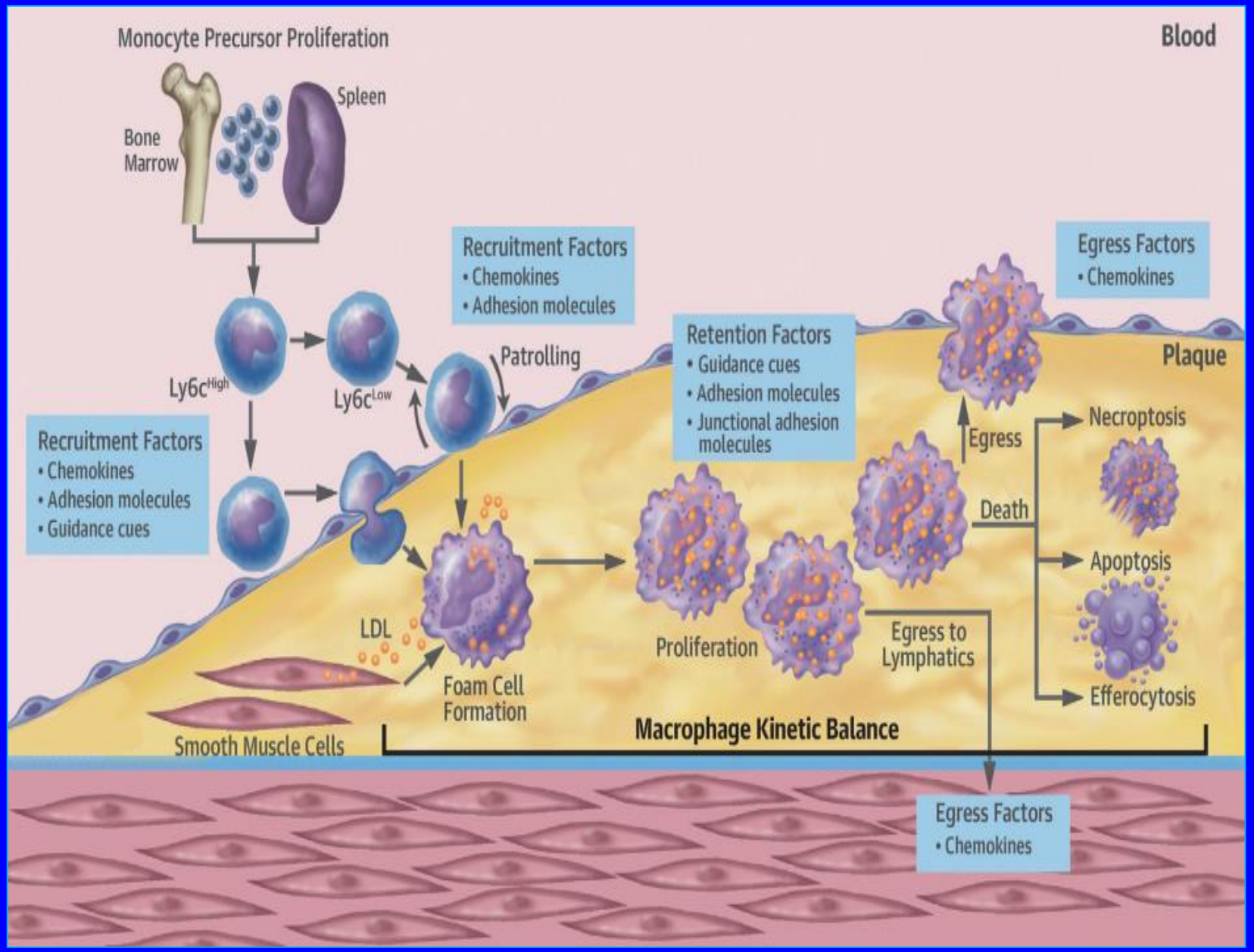
Circulation. 2017;135:476–489. DOI: 10.1161/CIRCULATIONAHA.116.025684

Macrophage LRP1 (Low-Density Lipoprotein Receptor-Related Protein 1) Is Required for the Effect of CD47 Blockade on Efferocytosis and Atherogenesis



Atherogenesis—Brief Report, Volume: 42, Issue: 1, Pages: e1-e9, DOI: (10.1161/ATVBAHA.121.316854)

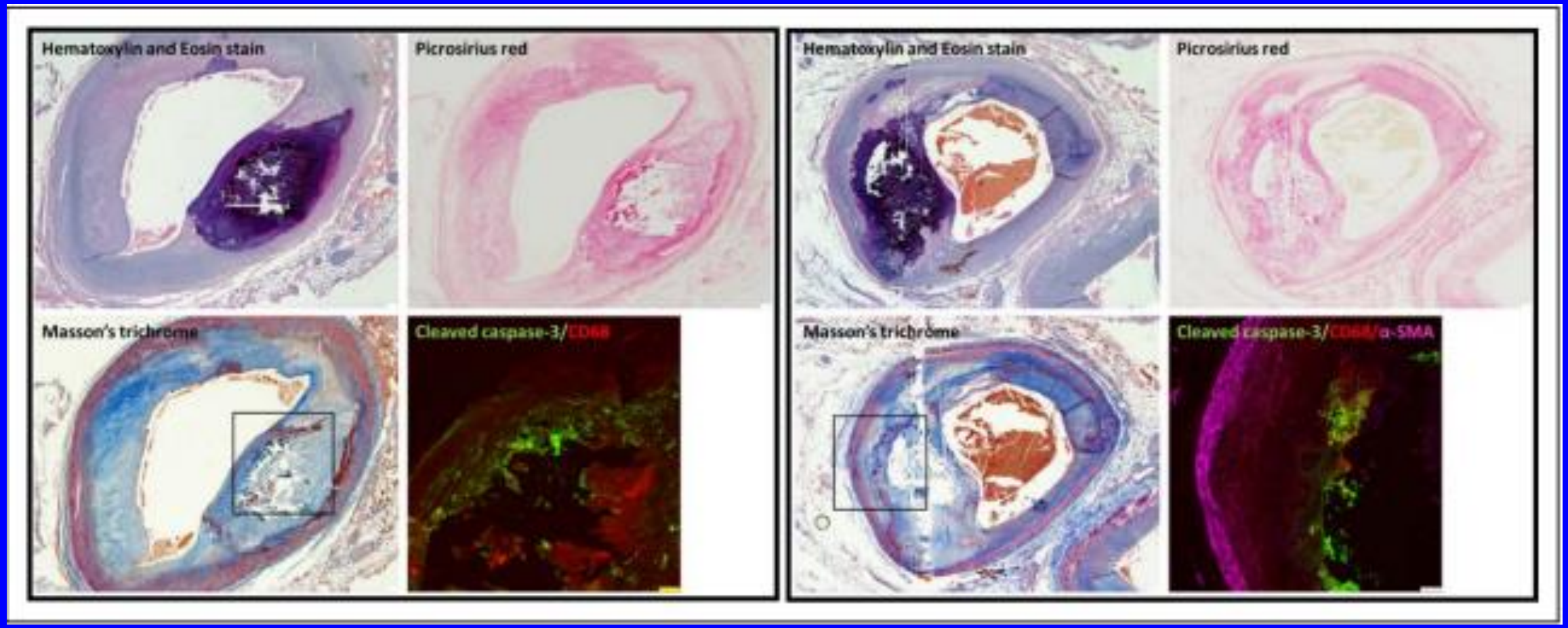
Macrophage Dynamics During Atherosclerotic Plaque Progression and Regression



Major kinetic processes dictating macrophage burden are recruitment of monocytes and the proliferation, retention, death, and egress of monocyte-derived macrophages. During hypercholesterolemia there is an increase in monocyte precursors in bone marrow and spleen, resulting in more circulating Ly6Chigh monocytes. Some become patrolling Ly6Clow monocytes, but the majority of monocytes recruited to plaques are Ly6Chigh, which transmigrate into the sub-endothelial space. In progression, these monocytes take up modified and retained lipoproteins, transforming them into inflammatory macrophage foam cells. Vascular smooth muscle cells can also become macrophage-appearing foam cells, but their properties and fates are largely undefined. In regression, recruited monocytes become M2, inflammation resolving, macrophages. In advanced plaques, macrophages can proliferate, and death by apoptosis and necroptosis can contribute to necrotic core formation, with falling levels of efferocytosis promoting core growth. In early plaques, reverse transmigration of macrophages may occur. This abates with progressing disease, but in regression, reverse macrophage transmigration can be restored by reduced retention and increased emigration factors.

Moore, K.J. et al. J Am Coll Cardiol. 2018;72(18):2181–97.

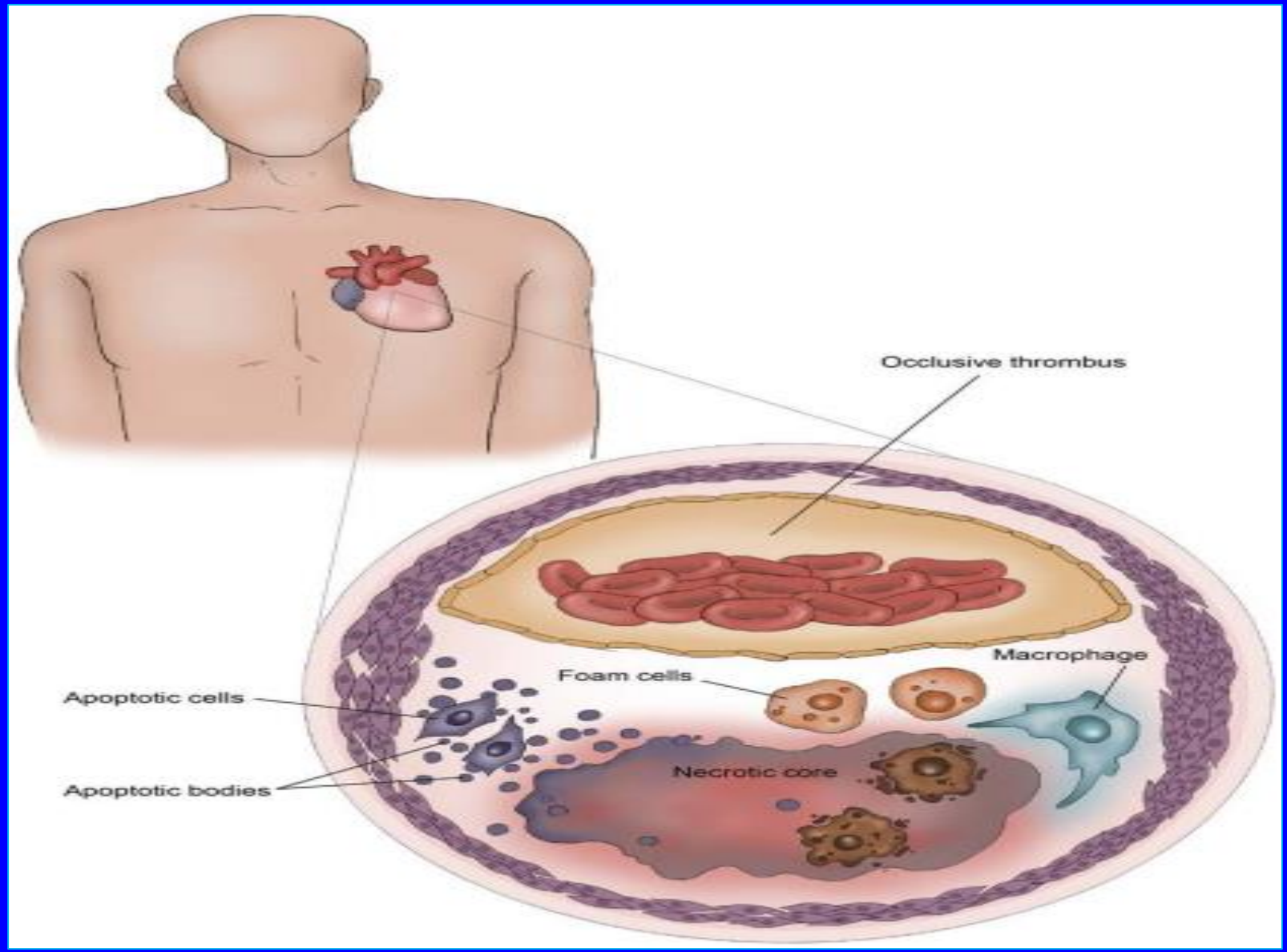
Examples of human atherosclerotic plaques



Examples of 2 human atherosclerotic plaques reveal that advanced lesions are frequently dominated by large necrotic cores. These necrotic cores tend to be replete with uncleared apoptotic tissue (noted with cleaved caspase-3 staining), which is not found in close proximity to lesional phagocytes (noted with staining for CD68). Thinning of the overlying fibrous cap (noted with picrosirius red staining) is also a hallmark of these vulnerable lesions, which presumably are prone to rupture due to inflammation present within the necrotic core.

Arterioscler Thromb Vasc Biol. 2022;42:e145–e154. DOI: 10.1161/ATVBAHA.122.317049

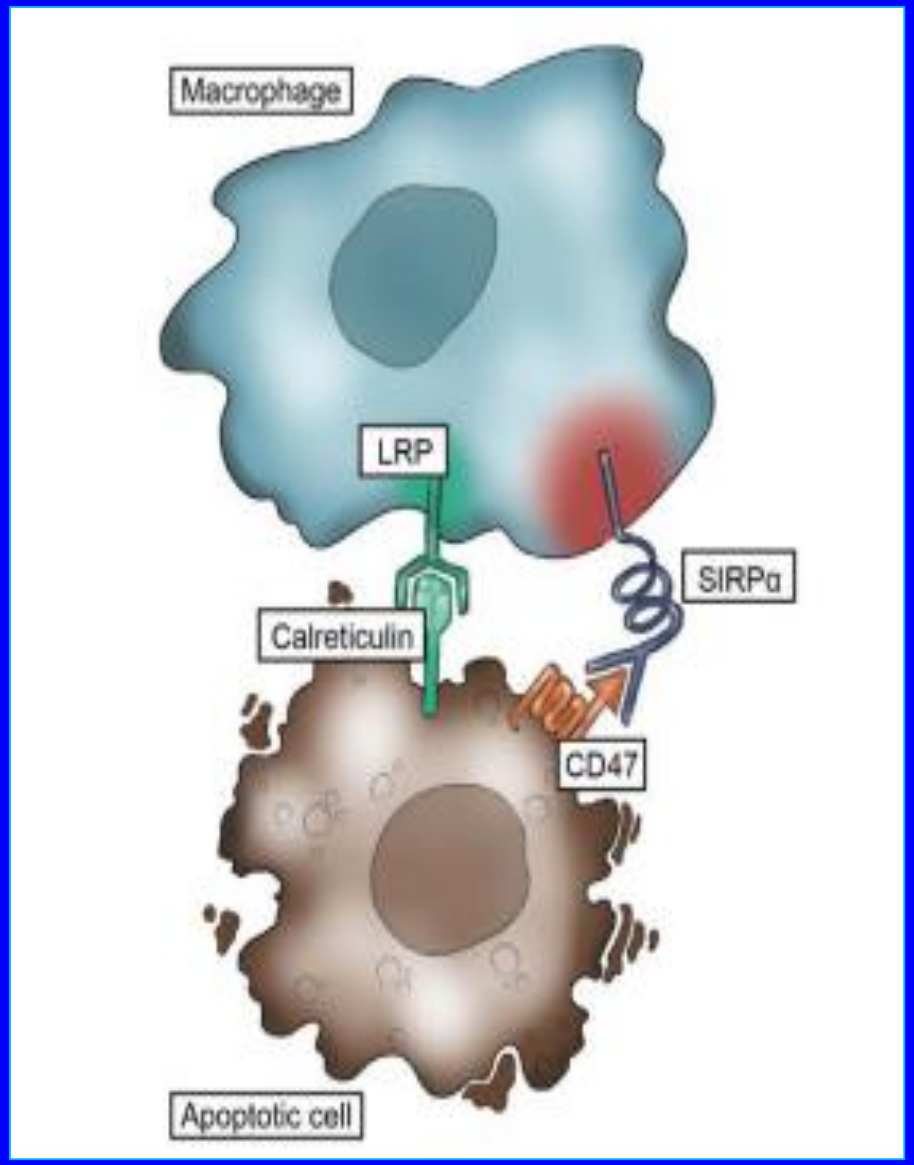
How impaired efferocytosis may promote atherosclerosis

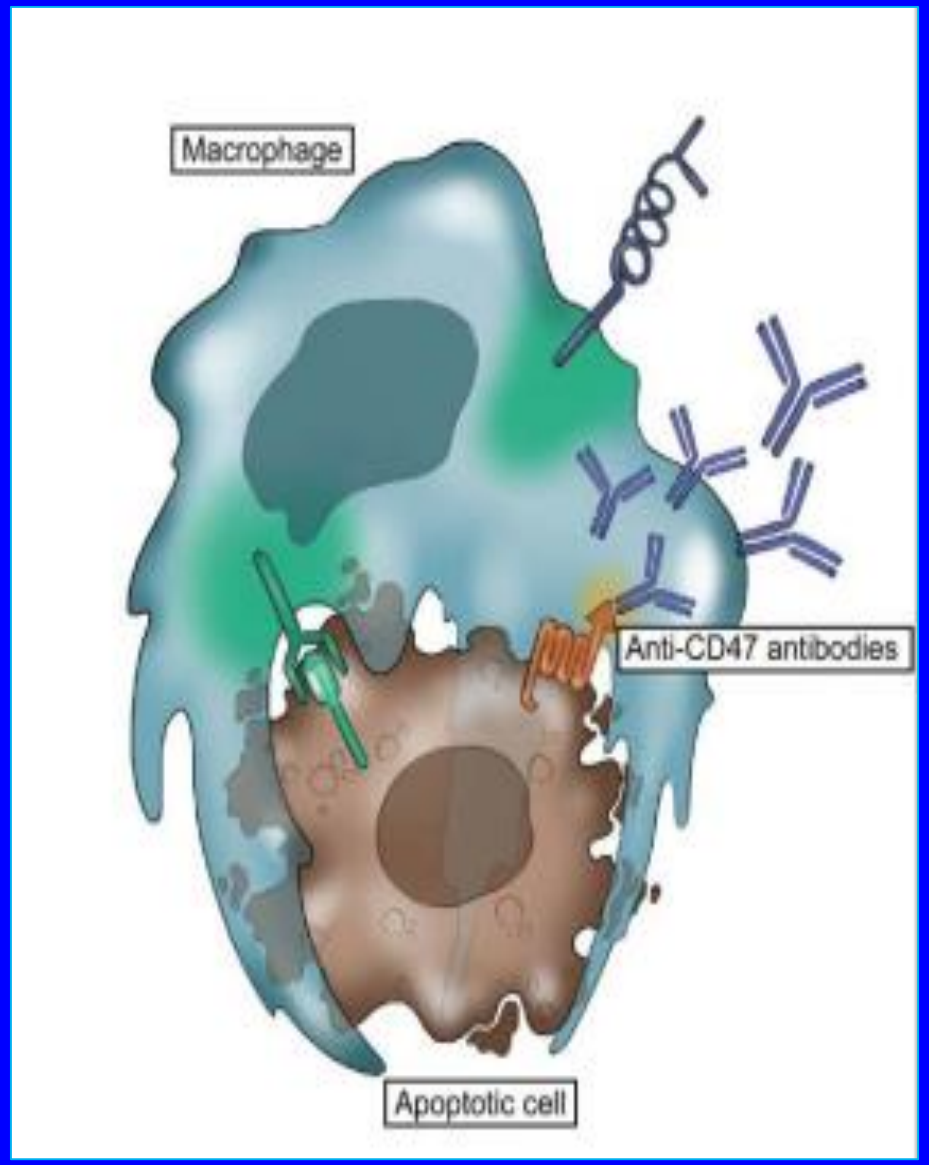


Lesional macrophages acquire a phagocytic defect during atherogenesis. Diseased and apoptotic cells, which have committed to programmed cell death, but are not rapidly identified for removal, sustain a breakdown in cell membrane integrity. Consequently, the necrotic debris, which accumulates in the growing plaque may not only promote the physical enlargement of the lesion, but also serve as a source of so-called danger signals that accelerate vascular inflammation, stimulate the recruitment of additional macrophages, and promote lesion instability.

Arterioscler Thromb Vasc Biol. 2022;42:e145–e154. DOI: 10.1161/ATVBAHA.122.317049

CD47 signaling in efferocytosis





Many pro efferocytic stimuli are thought to be fine-tuned by counterbalancing do not eat me signals.

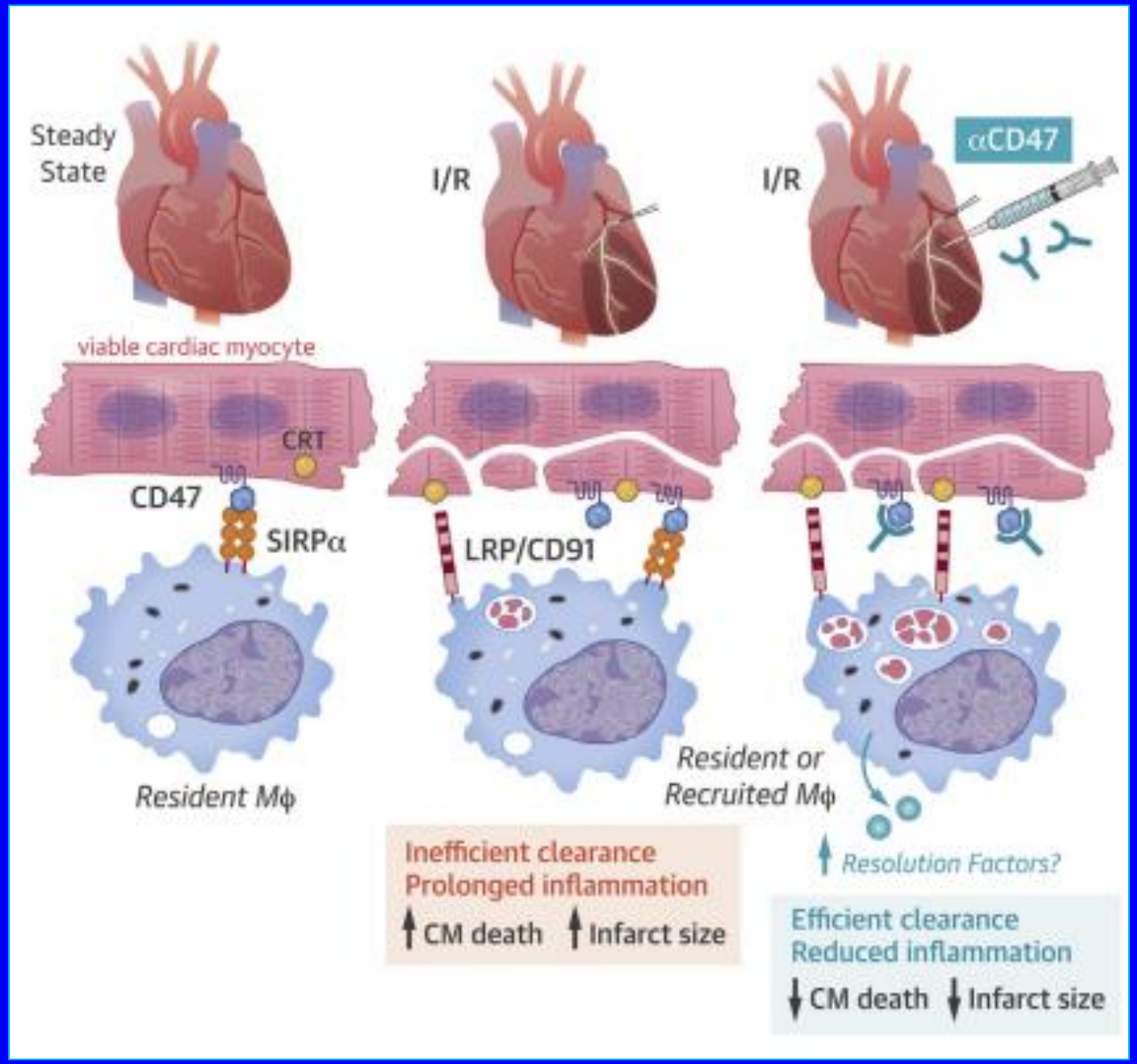
Experimental data suggest that prophagocytic signals (including calreticulin which promotes phagocytosis via its receptor LRP1 [low-density lipoprotein receptor related protein 1]) are reduced in atherosclerosis.

In parallel, the pathological upregulation of the key *do not eat me* molecule CD47 (which inhibits engulfment via its receptor SIRPα [signal regulatory protein alpha]) further decreases the edibility of diseased and dying cells within the necrotic core.

However, inhibition of CD47-SIRPα signaling by antiCD47 antibodies restores impaired efferocytosis and thus represents a new therapeutic target in atherosclerotic cardiovascular disease.

Arterioscler Thromb Vasc Biol. 2022;42:e145–e154. DOI: 10.1161/ATVBAHA.122.317049

Acute CD47 Blockade During Ischemic Myocardial Reperfusion Enhances Phagocytosis-Associated Cardiac Repair



New therapies are needed to enhance myocardial salvage after myocardial ischemia and reperfusion.

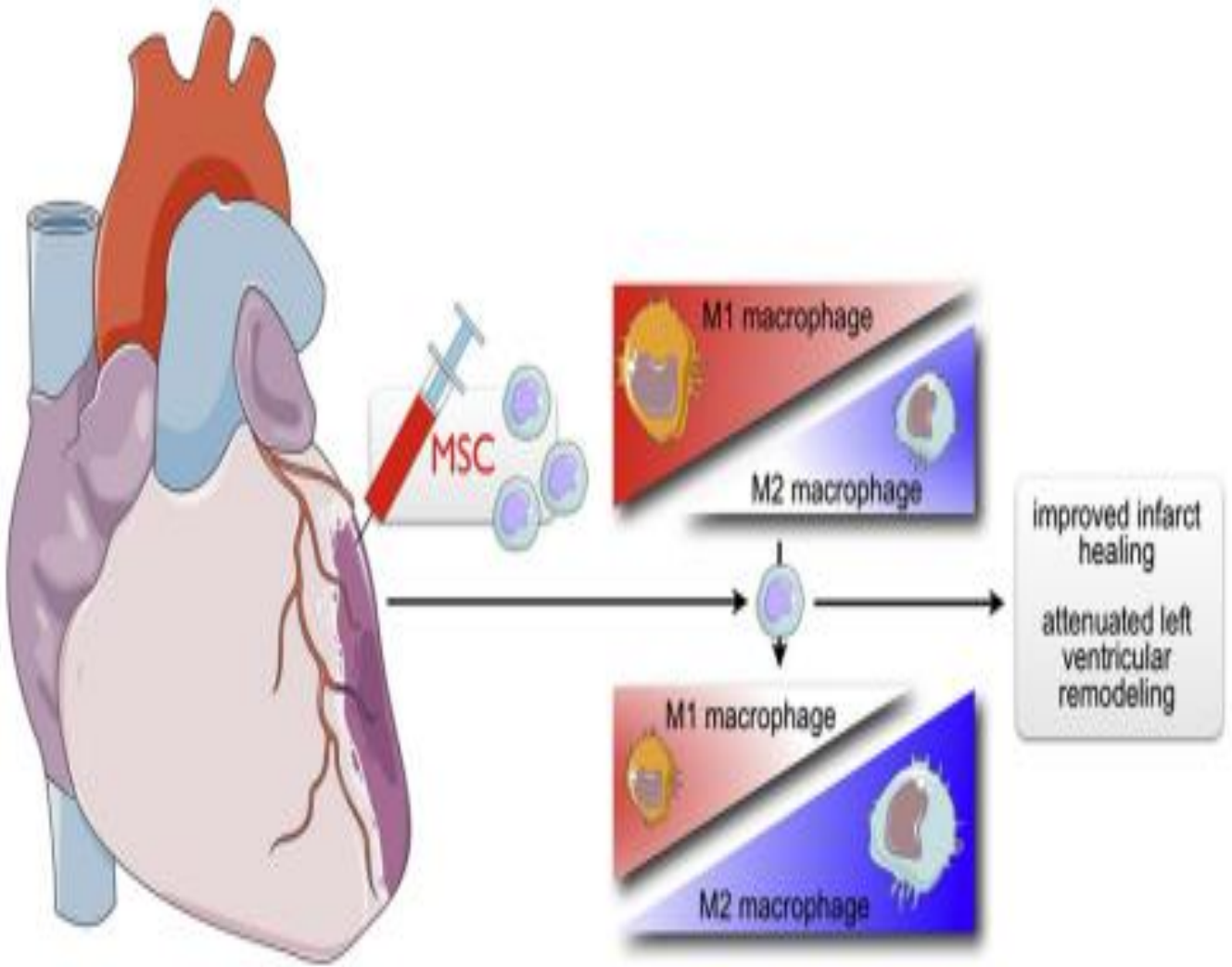
Human and murine hearts express CD47 and calreticulin that increased after ischemia and reperfusion.

Phagocytic efficiency of dying cardiac myocytes was enhanced after antibody-mediated blockade of either myocyte CD47 or macrophage CD47-ligand, SIRPa.

After ischemia and reperfusion, enhancement of dead myocyte clearance by macrophages, after CD47 blockade, improved inflammation resolution, reduced infarct size, and preserved cardiac systolic function

J Am Coll Cardiol Basic Trans Science. 2017;2(4):386–97.

Modulation of Macrophage Polarization by MSC Injection



The MSC injection increased the numbers of M2 macrophages as compared to saline or bone marrow mononuclear cell injection. The treatment further changed the cytokine profile of macrophages (e.g., more IL-10 production) and increased the elaboration of macrophage-derived factors involved in wound healing, including VEGF and platelet factor-4. Proteolytic cathepsin activity was reduced by MSC treatment, which may change the post-MI balance of matrix production and its digestion by proteases favoring infarct stability.

When Ben-Mordechai et al. (11) depleted macrophages with clodronate liposomes, the beneficial effects of MSC treatment were lost.

The 30-day mortality was worse and infarct size increased.

Journal of the American College of Cardiology Vol. 62, No. 20, 2013, https://doi.org/10.1016/j.jacc.2013.07.058

Reference
1.Circulation Research 2019. 125:(8) 728-743, DOI: 10.1161/CIRCRESAHA.119.315432)
2.Cell Research (2020) 30:1057–1058; https://doi.org/10.1038/s41422-020-00427-z
3.Front. Immunology. 12:669891. DOI: 10.3389/fimmu.2021.669891