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Previews

Mitochondrial Ejection for Cardiac Protection: The Macrophage Connection

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Mitochondrial dysfunction is a hallmark of heart disease. Nicolás-Ávila et al. (2020) now find that cardiomyocytes eject dysfunctional mitochondria in exopher vesicles, which require elimination by specialized heart-resident macrophages, altogether supporting proper heart function.

The heart has remarkable metabolic activity, relying on a continuous supply of oxygen and nutrients. Cardiomyocytes have very little cellular turnover and limited regenerative capacity, even though they have a lifelong responsibility for carrying out their demanding role. Central to the function of cardiomyocytes is the very high mitochondrial content and oxidative metabolism, but interestingly, canonical pathways of mitochondrial quality control seem to be hampered by the hypo-dynamic, disconnected nature of cardiomyocyte mitochondria when compared to the continuous fission and fusion observed in many other cell types (Dorn, 2015).

Nicolás-Ávila et al. have now discovered a novel mechanism by which cardiomyocytes sustain mitochondrial quality and heart function (Nicolás-Ávila et al., 2020). Unexpectedly, they found that cardiomyocytes rely on a network of resident cardiac macrophages (cMacs) for clearing dysfunctional cellular parts through so-called exophers—an ejection mechanism for large vesicular particles previously described in *C. elegans*, with unclear mammalian relevance to date (Melentijevic et al., 2017). Using an imaging strategy with genetic labeling, Nicolás-Ávila et al. identified that—under normal conditions in the working heart, in the absence of any heart disease or other pathogen-induced inflammation—macrophages are abundant in the ventricular areas and are in close contact with cardiomyocytes, so much so that each cardiomyocyte has several macrophages standing by *en garde*.

In principle, this finding is not entirely unprecedented, as heart-resident macrophages have been implicated in several homeostatic processes and, most notably, during critical disease conditions (Swirski and Nahrendorf, 2018). However, when Nicolás-Ávila et al. acutely ablated CD169/Siglec1-positive cMacs in mice, they observed that cardiomyocytes were stressed, and functionally compromised, yet surprisingly their mitochondrial content was increased. Further analyses showed that in the absence of cMacs, cardiomyocyte mitochondria displayed aberrant metabolic flexibility and produced less ATP, which is of critical importance, as after a few heartbeats ATP stores are depleted (Dorn, 2015). This was also associated with transient generalized heart dysfunction, which recovered once cMacs had repopulated the heart. So what is the function of cMacs in sustaining metabolism of the heart? Nicolás-Ávila et al. found that cMacs phagocytosed exophers containing mitochondrial scrap, which cardiomyocytes generated through autophagy, as shown by blocking autophagy both pharmacologically and genetically. In the absence of cMacs or in mice lacking the phagocytic receptor Mertk, exophers accumulated in the extracellular space of the myocardium. An efficient exopher removal by efferocytosis was required to prevent inflammasome activation, intracellular autophagic jamming, and aberrant mitochondrial function (Figure 1).

The implication of exopher shedding as an alternative mechanism of cellular quality control in the heart raises several mechanistic questions and novel research avenues. Cells that are structurally and functionally unique and so specialized that they might not have the capacity for common self-renewal and regenerative pathways seem to rely on waste disposal mechanisms. As cardiomyocytes are continuously working, it might be advantageous for the cells to just throw out cellular junk. Similarly, brown adipocytes rely on proper waste management by proteasomal protein degradation as a major adaptive quality-control approach (Bartelt et al., 2018). It will be exciting to explore exopher shedding in other cell types like brown adipocytes, skeletal myocytes, or neurons, all of which display high mitochondrial content and are highly metabolically active. Also, how materials become designated for ejection as well as the molecular details of exopher formation within cardiomyocytes by engaging the autophagy machinery warrant further exploration. Another relevant issue is how cMacs are attracted to the sites of exopher formation, which the authors have shown to be toward the edges of cardiomyocytes. Is this only mediated by a gradient of exophers, which display phosphatidyl serine flashing, a well-established phagocytic signal, or are other signals,

e.g., chemokines, also involved in maintaining the population of cMacs?

It will require comprehensive lineage tracing and fate mapping studies to determine how embryonically versus adult (CCR2-dependently) derived cMacs compare in their propensity for exopher clearance at steady state and during inflammatory stress, with the latter displaying limited efferocytosis capacity (Epelman et al., 2014). While the function of CD169^{+} cMacs appears to be tissue specific, as their depletion did not affect mitochondrial content of the liver, it remains to be determined whether subsets of resident CX$_3$CR1- and CD115-driven macrophages with related or specifically adapted functionality exist in other tissues. For instance, normal arteries are also colonized by resident macrophages, which can arise embryonically but mostly by a postnatal wave of bone marrow-derived monocytes (Ensan et al., 2016; Williams et al., 2020). These cells are likewise sustained by limited local proliferation and represent the earliest foam cells during atherosclerotic plaque formation (Williams et al., 2020). Given the current findings that resident cMacs can also incorporate cargo from endothelial cells and that mitochondria are a preferential, but not exclusive, organelle constituent of exophers, similar mechanisms may also be operative in maintaining the integrity of arteries, where autophagy essentially contributes to the homeostasis of distressed endothelial cells under atherogenic conditions (Santovito et al., 2020).

From a therapeutic perspective, perhaps the most intriguing future area of investigation is understanding the relevance of exopher formation in human heart disease, as it is causally linked to aberrant cardiac metabolism, and most notably mitochondrial dysfunction (Swirski and Nahrendorf, 2018). Nicolás-Ávila et al. have shown that in principal, cMacs and exophers are found in human heart tissue, but their pathological significance is still unclear. In mice, they provided evidence for a cardioprotective role for cMacs in response to ischemia-reperfusion injury. Further, how the population of cMacs is recruited, maintained, altered, or negatively impacted in composition and function by cardiac inflammation, and how this relates to other homeostatic roles, e.g., in electrical conductance, under pathological conditions will be important to address. The dynamic nature of cMac action and its cardioprotective effect might suggest that molecular approaches enhancing cMac activity when cardiomyocytes are stressed, for example after a myocardial infarction, might have therapeutic value.

In conclusion, Nicolás-Ávila et al. have uncovered a quality-control mechanism by which cells of the immune system contribute to metabolism with exciting biological implications and potential therapeutic value for various heart diseases.

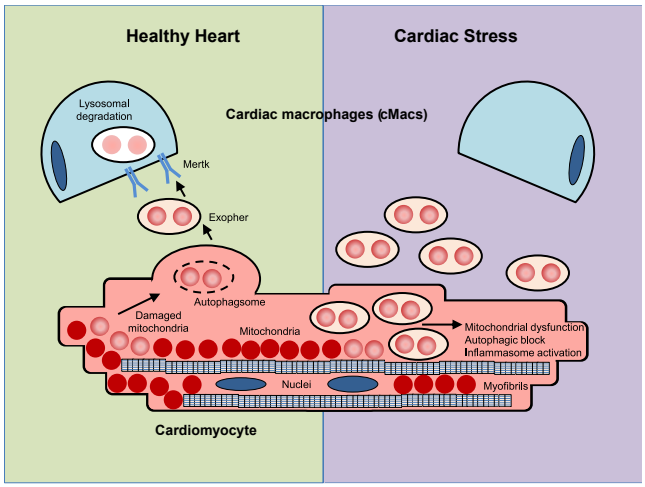

Figure 1. Interaction between Cardiac Macrophages and Cardiomyocytes for the Clearance of Exopheres Carrying Dysfunctional Mitochondria
Mertk, Mer tyrosine kinase.

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