Resident cardiac macrophages are involved in cardioprotection through metabolic regulation of cardiomyocytes

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In Japan, the number of heart failure patients is expected to increase from now on. So, how to prevent or cure heart failure is a pressing issue. Recent studies have reported that resident macrophages in the heart maintain cardiac function. However, it isn't sufficiently understood how cardiac macrophages are involved in cardioprotection. Since heart failure involves myocardial metabolic disorders, here we hypothesized that cardiac macrophages might control myocardial metabolism by amphiregulin (AREG). Cardiomyocytes mainly oxidize fatty acids to make ATP, but under stress, they use glycolysis instead of fatty acids. This metabolic flexibility is thought to be important for maintaining myocardial homeostasis and preventing heart failure. AREG activates pyruvate dehydrogenase (PDH), an enzyme that regulates entry into the TCA cycle from the glycolysis. PDH is phosphorylated by Pdk4 and dephosphorylated by Pdp2, and dephosphorylated form is active form. The expression level of Pdk4 decreased and that of Pdp2 increased by AREG. These days suggest that AREG enhances the flow of the substrate from the glycolysis to the TCA cycle by activating PDH. Therefore, AREG regulates the metabolism via PDH in cardiomyocytes. In other words, cardiac macrophages protect cardiac function by regulating myocardial metabolism.