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Monocyte activation after myocardial infarction: the role of non-canonical WNT signaling and WNT Inhibitory Factor-1

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An exaggerated inflammatory response following myocardial infarction (MI) is associated with poor prognosis and increased tissue damage that may lead to the development of heart failure. Monocytes have been shown to be crucial for an adequate healing process following MI, but little is known about the role of the cardiac niche in monocyte activation.
RNA sequencing analysis of inflammatory monocytes in a murine model of MI revealed differential regulation depending on location. Especially components that were associated with the WNT signaling pathway were strongly impacted. Monocytes isolated from infarcted myocardium showed more non-canonical WNT signaling than monocytes from bone marrow or blood. In contrast, canonical WNT signaling activity was downregulatedin cardiac monocytes compared to their bone marrow- and blood-derived counterparts. These dynamics were corroborated in vitro: supernatant from hypoxic cardiomyocytes activated non-canonical WNT signaling in myeloid cells while canonical WNT signaling was downregulated.
The WNT antagonist WNT Inhibitory Factor 1 (WIF1) has not been studied in the context of MI. Increased levels of WIF1 were detected in the days following MI and cardiomyocytes appear to be the crucial source. Compared to wild type (WT) littermates, WIF1 knockout mice showed severe adverse remodeling marked by increased scar size and reduced ejection fraction after MI. While FACS analysis revealed no differences in neutrophil numbers, the hearts of WIF1 knockouts contained significantly more inflammatory monocytes than hearts from WT animals during the inflammatory phase of infarct healing. Induction of AAV-mediated cardiomyocyte-specific WIF1 overexpression attenuated the monocyte response and improved cardiac function after MI, as compared to control-AAV-treated animals. Finally, WIF1 overexpression in isolated cardiomyocytes limited the activation of non-canonical WNT signaling and led to reduced IL1β and IL6 expression in monocytes/ macrophages.
Taken together, these results are the first description of the cardiac microenvironment's interaction with recruited monocytes after MI. The local activation of non-canonical WNT signaling shifts the accumulating myeloid cells toward a pro-inflammatory state and impacts healing after MI.