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Myocardial extracellular matrix during post-infarction remodeling: The role of C3-complement system

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Background: Healing of the myocardium or progression to heart failure following myocardial infarction (MI) seems directly related to dynamic changes in protein composition of the extracellular matrix (ECM). The myocardial matrisome, fraction of functional non-structural ECM-associated proteins (ECMm), may regulate myocardial remodeling post-MI but the mechanisms involved remain unknown. We identified the C3-complement system (C3-CS), a central effector pathway of the innate immune system, and cleavage products by proteomic analysis of porcine myocardial tissue post-MI. Here we investigated the C3-CS dynamic changes in the myocardial ECMm of reperfused hearts in relation to the ischemic zone and time of evolution post-MI.

Methods: ECMm proteins were investigated in the ischemic (ISCH) and non-ischemic (NISCH) zones in the porcine myocardium Post-MI. MI was induced by closed-chest balloon occlusion of the LAD for 90 minutes. Myocardial tissue was obtained after 2.5h, 1d, 3d and 30d after MI ((n=7/time-point). ECMm was extracted and C3-CS protein signature analyzed by western blot with specific antibodies. Myocardial tissue from the same areas was characterized by immunohistochemistry (IH).

Results: C3-cleavage products derived from activated C3-CS and its regulatory proteins (CFD, CFH, and CFHR5) were consistently detected in post-MI myocardium with a differential protein-signature between ISCH and NISCH zones and changed dynamically with elapsed time post-MI. The major changes were detected in the ISCH zone that was enriched with innate immunity cells (neutrophils and macrophages) as seen at day 3 by IH, suggesting local rather than systemic induction of C3-activation. Thus, CFD (C3-activating factor) and CFHR5 (C5-convertase inhibitor) were significantly increased in ISCH ($>$2fold vs. NISCH) at day 1, resulting in a high generation of the chemotactic and inflammatory C3a-product. At day 3, there was a high content of macrophages ($>$5fold higher than 24h) in the ISCH zone with enrichment of iC3b-products ($p<0.05$ vs. NISCH zone) derived from CFI/CFH-induced cleavage of C3b. In contrast, at day 30, there was enrichment in fibroblasts and collagen fibers in the ISCH zone and an increased C5-activation pattern compared to all the earlier times (2.5–24 h) and the NISCH zone. Thus, C5b, main source of the called "membrane attack complex" was significantly elevated and CFHR5 reduced compared to values at day 3.

Conclusion: Our results evidenced a time-dependant coordinated response of the C3-System in the ECMm of the ischemic myocardium, starting shortly after reperfusion and maintained up to 30 days that parallels changes in the cell pattern present in the ISCH zone. Our results show that C3-CS is associated to key cell functions for tissue remodeling and repair.