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M2 cardiac macrophages in wound healing following myocardial infarction: translation to clinic

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Introduction. Macrophages play a significant role in transition from inflammatory to regenerative phase during wound healing following myocardial infarction (MI). Despite the progress of experimental investigations on the innate immune response following MI, there is no significant advancement in clinical studies.

Purpose. The purpose of the research was to translate experimental knowledge regarding M2 macrophage subsets and their biomarkers in post-infarction left ventricular remodeling and myocardial regeneration into results observed in clinical settings. We suggested protocol based on usage of macrophage biomarkers (scavenger receptors) to study cellular basis of cardiac remodeling in patients with MI.

Methods. The study included 41 patients with fatal MI type 1. All patients were divided into 4 groups depending on the timeline of MI histopathology. In addition to routine histopathological analysis macrophages infiltration was assessed by immunohistochemistry. We considered CD163 as a commonly used marker of M2 macrophages and stabilin-1 as a supplemental M2 macrophage biomarker. Nine patients who died from non-cardiovascular causes comprised the control group.

Results. The figure (Figure 1) demonstrates results of immunohistochemical analysis. In the control group the number of CD163+ macrophages was lower than in the infarct, peri-infarct and non-infarct areas during all phases of MI (p<0.001). Simultaneously the quantity of stabilin-1+ cells in the control group was higher in all the areas during inflammatory phase of MI (p=0.01). We noticed that numbers of CD163+ and stabilin-1+ macrophages depended on MI phase. The number of CD163+ cells correlated with the day of MI: positive correlation was found in the infarct (R=0.61, p=0.001) and peri-infarct areas (R=0.66, p<0.001). There was similar relationship for stabilin-1+ cells (infarct area: R=0.6, p<0.001; peri-infarct area: R=0.42, p=0.007).

Conclusions. Our study translated experimental knowledge regarding M2 macrophages in post-infarction myocardial regeneration into clinical. We observed cardiac macrophage response following MI reminded a murine model. The difference consisted in a prolonged high-grade CD163+ and stabilin-1+ macrophage infiltration during the late phase of MI. Our data indicate following: (1) dichotomous M1-M2 model is not sufficient to completely describe functions of macrophage subsets due to their heterogeneity; (2) characterization of macrophage phenotypes by multiple biomarkers is a promising conception; (3) stabilin-1 could be used as macrophage biomarker in cardiac wound healing in patients with MI. Our study supported diagnostic prospects for implementation of macrophage phenotyping in clinic. Identifying effective biomarkers of macrophage subsets in patients with MI might become the first step to develop myocardial regeneration target therapy.
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Figure 1. Dynamics of CD163+ and stabilin-1+ macrophage infiltration. The vertical axis represents the number of cells. The number of CD163+ macrophages is significantly higher than number of stabilin-1+ cells (p<0.05). Group 1 (n=13) comprised patients who died during the first 24 hours of MI; group 2 (n=11) - patients who died within 24-72 hours of MI; group 3 (n=9) - patients who died on days 4-10 after MI; group 4 (n=8) - patients who died on 11-28 days after MI.