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New Therapeutic Strategies for Ventricular Remodeling in Acute Myocardial Infarction and Pressure Overload: The Long Way to Heaven

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Despite the striking improvements recently achieved in the diagnosis and treatment of acute myocardial infarction (AMI), this condition remains a leading cause of death worldwide [1]. The term "ventricular remodeling" refers to changes in ventricular geometry (dilation, sphericity, wall thinning) and stiffness, as well as molecular and functional changes including both cardiomyocytes , other cells of the heart and extracellular matrix [2,3]. As a result, over recent years much interest has been devoted to understanding the role and the pathways involved in the setting of the inflammation in AMI as well as in overload conditions [4] but to date, however, there is a lack of real anti-inflammatory treatments for these conditions. This topic has been recently highlighted by Seropian et al., in a detailed paper [5] focusing on anti-inflammatory strategies for ventricular remodelling following ST-segment elevation myocardial infarction (STEMI), concluding that more studies are needed to determine the most appropriate strategies to restore the inflammatory balance and ameliorate remodelling after acute myocardial infarction (AMI). This holds even truer given the established heterogeneity among different anti-inflammatory agents, as clearly demonstrated in many different pathophysiologic conditions [5,6]. We agree that this entire process should be considered as a complex biological *milieu* finally evolving into maladaptive remodelling, with the result to be still a slippery therapeutic target. Nonetheless, the report raises additional issues that need to be addressed in order to enlighten the corresponding hidden side of the moon.

First, the recent demonstration that cardiomyocytes are not terminally differentiated cells with the capacity to re-enter the cell cycle even in AMI models and the finding of a cardiac stem cell (CSCs)-associated paracrine enhancement in tissue preservation and recruitment of endogenous repair [7,8], strongly suggest that CSCs also might be involved in determining which patients respond favorably or not to early reperfusion strategy in routine clinical practice. The concept of the heart considered as a "dynamic environment" responding to multifaceted stimuli seems also to be corroborated by several studies concerning mechanical unloading achieved by Left Ventricular Assist Devices (LVAD) [9,10] in which CSCs seem to significantly contribute in the recovery of cardiac function and in the substantial reverse remodeling occurring during LVAD support. Last a key role to be fully exploited in the modulation of heart inflammation toward anti-remodeling strategies maybe represented by the synergistic combination of cardiac stem cells therapy and tissue engineering (TE): this hopeful union seems thus to boost the sole protective role achieved from stem cells or TE in limiting myocardial remodeling [3,11]. It seems likely that, stem cell therapy joined with TE technology, will occupy within the next decade a significant place in the treatment of several cardiovascular diseases. Accordingly an accurate intertwining of muscle/extracellular matrix re-growth, inflammation, and angiogenesis, coupled with changes in cardiac metabolic profile, may be pivotal to ensure adaptive remodelling in both conditions, AMI as well as overload conditions CSCs [12].

Once more, focusing deeply on this topic, it is noteworthy to emphasize the key role of other important mediators in the recovery of cardiac function following AMI and overload conditions: cytokines, integrins, proapoptotic genes, MMPs, PI3K, complement cascade, reactive oxygen species (ROS), micro-RNA [13] mediating post-transcriptional gene silencing and last, the possible role of epigenomic changes that can explain a characteristic hallmark of heart failure (HF), i.e. altered gene expression. The cardiac environment under conditions of stress such as ischemia and overload may therefore promote epigenomic changes with a subsequent plasticity in gene expression and phenotype leading to hell as well as to heaven.

In conclusion, all these fields of research arise important questions of potential clinical impact as this complex picture is strongly supportive of a pivotal role of many factors in establishing an adequate and necessary inflammatory response to several pathological conditions.

Besides the discrepancies among different evidences reported about the efficacy of cardiac anti-inflammatory therapies, we believe that it will be paramount to carry out a gnoseological step-back to identify a representative cohort of patients in order to provide new important insights into physician patterns of practice related to recovery therapies, allowing customized strategies to be targeted to each specific patient.

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Patent: US 20120021019 A1, 2012-01-26 - Giacomello A., Messina E., Battaglia M., Frati G, Cardiac stem cell populations for repair of cardiac tissue- Owner: University of Rome "Sapienza").

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