Factor XIII: the cement of the heart after myocardial infarction?

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This editorial refers to ‘Transglutaminase activity in acute infarcts predicts healing outcome and left ventricular remodelling: implications for FXIII therapy and antithrombin use in myocardial infarction’ by M. Nahrendorf et al., on page 445

Heart failure (HF) affects >11 million people in the USA and Europe, and ischemic heart disease accounts for >60% of these patients. Despite excellent diagnostic and therapeutic standards for myocardial infarction (MI), improved early phase imaging and therapy are essential to prevent the progression of cardiac dilatation and dysfunction after acute MI.

Transglutaminases (TGs) are a widely distributed group of eight isoenzymes, comprising factor XIII (FXIII) and TG type 1–type 7. They catalyse the post-translational modification of matrix proteins by the formation of isopeptide bonds, either via ε-lysyl–γ-glutamyl cross-links, or through incorporation of primary amines at selected peptide-bound glutamine residues. Collagens, fibronectin, fibronogen, vitronectin, osteopontin, and osteonectin are the major substrates in the cardiac matrix. Their cross-linking strengthens the matrix and prevents their degradation. Dysregulation of TG activity after MI therefore results in abnormal collagen fibrillogenesis, with resulting cardiac dilatation and dysfunction.

FXIII, also called fibrin-stabilizing factor, is a pro-TG present in plasma, platelets, monocytes, and macrophages. Its pro-form is converted by a thrombin-dependent proteolysis into the active TG FXIIa. The latter also catalyses the formation of covalent bonds between fibrin monomers, the final step of the blood coagulation pathway. Beside its role in this cascade, it also appears crucial for wound healing and tissue repair, in particular after MI. FXIII-deficient mice had increased fatal left ventricular wall rupture and dysfunction after MI, whereas FXIII replacement was protective. FXIII thus mediates the formation of a well-cemented scar, essential for structural and functional recovery after MI.

In the study of Nahrendorf et al., the research group attempted to translate these animal findings into a potential therapeutic impact of TG modification for human MI. Concordant with increased cardiac rupture in the absence of FXIII, its expression levels were significantly diminished in myocardial biopsies of human ruptured MI. In addition, reduced FXIII activity imaged via single photon emission computed tomography (SPECT)–computed tomography (CT) predicted adverse infarct healing after MI in mice. In contrast, increased intracardiac FXIII activity via induction of high FXIII zymogen plasma levels improved cardiac healing, whereas decreased FXIII activity by deltaperin treatment caused impaired infarct healing and increased mortality after MI. An important question arising from this work is whether imaging of cardiac FXIII activity after MI may provide a novel non-invasive tool to assess infarct healing and left ventricular remodelling, and predict its prognosis in daily practice. Another issue is whether FXIII treatment could protect against cardiac dilatation and failure.

In clinical practice, we definitely need novel therapeutic tools that strengthen the infarct scar and prevent adverse left ventricular remodelling and dilatation within the first days after MI. Here, FXIII therapy enhanced recruitment of inflammatory cells, increased vascular endothelial growth factor (VEGF) expression, augmented angiogenesis, and increased collagen synthesis, all together protecting against HF after MI. These data indicate that increased FXIII/TG activity after MI is not an innocent bystander, but a helper protein that cements the infarcted heart and improves its functional outcome. These finding are concordant with our previous findings, revealing increased cardiac dilatation and dysfunction caused by decreased tissue TG activity in syndecan-1-null mice after MI. A superior quality of the cardiac matrix—rather than increased quantity—is a requisite for the maintenance of structural and functional integrity after MI. Together with the matricellular proteins thrombospondins, osteopontin, and osteoprotegerin, TGs may provide novel therapeutic targets to improve matrix maturation and strengthening of the infarcted heart within the first days after MI.

One limitation of this study, however, is that the mouse model of permanent ligation of the coronary artery does not take into account the well-known anti-thrombotic benefits of heparin and the pro-thrombotic effects of FXIII. In patients, MI requires anti-thrombotic therapy of the occluded vessel, and heparin is a standard treatment in patients with an acute coronary syndrome.
initiated by plaque rupture and thrombus formation. In the study of Nahrendorf et al., non-physiological doses of heparin were used to delineate its effect on FXIII activity and wound healing after MI in mice. Therefore, the clinical relevance of its adverse effect on infarct healing in mice should be considered with care. We also cautiously need to keep in mind that FXIII stabilizes blood clots, which is an undesirable effect in unstable plaques. Use of FXIII in a clinical setting after MI could therefore have detrimental consequences. More definitive conclusions on the role of FXIII modulation after MI will require further animal studies. A modified FXIII protein that increases TG-mediated cementing of the heart without affecting clot formation should be designed. This modified protein could reinforce the heart and prevent cardiac dilatation after MI. What would be a reasonable therapeutic time frame to improve wound healing with this tool? How could we monitor the effect of such a new and altered FXIII/TG therapy on local cardiac FXIII activity and matrix quality after MI?

Molecular imaging of FXIII activity for the assessment of wound healing and the prediction of prognosis after MI is another opportunity of this study. In medical practice, a combination of clinical exam, electrocardiograms, circulating biomarkers, and imaging is used to gain insights on the prognosis after MI. Novel molecular non-invasive imaging tools are needed that help clinicians to assess wound healing and prognosis, and thereby achieve improved therapy for the prevention of dilatation and dysfunction immediately after MI. Molecular imaging of cardiac FXIII activity might give us the ‘glasses’ to look into the heart and provide information on scar maturation and related prognosis after MI.

In conclusion, imaging of FXIII activity and therapeutic use of its TG properties may offer a new diagnostic and treatment strategy after MI. Future research within the MI field will focus on the underexploited time window between reperfusion and scar formation after MI, leading to early interventional therapeutics that ‘cement’ the infarcted hearts and prevent HF.

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References


