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The key function of Frizzled1 in modulating wound healing following acute myocardial infarction

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Myocardial infarction (MI) is a major cause of morbidity and mortality in the western countries. During the wound healing process after MI, Wnt signaling has been verified to play a crucial role. Frizzled1 (FZD1) is suggested to serve as a receptor in the canonical Wnt signaling. Recently, growing evidence demonstrates that Frizzled1 is an important participant in the process of myocardial remodeling. Moreover, we found that FZD1 was modulated after MI in both mouse heart tissue and human serum. Therefore, in this study, we investigated the role of FZD1 in the wound healing process following MI and the underlying mechanisms.

Since vaccination also referred to pre-immunization is a widely used strategy to prevent or treat diseases, A/J mice were subcutaneously injected with either recombinant mouse FZD1 protein or control buffer to induce immune response against FZD1. Afterwards, sham or MI operation was induced to these mice. Notably increased FZD1 autoantibodies in plasma samples were observed in FZD1 pre-immunized mice compared to control buffer injected group. Interestingly, these FZD1 autoantibodies induced the upregulation of FZD1 receptors. Moreover, increased expression of active β-catenin as well as p-Gsk-3β (Ser9) was observed, which suggested the activation of canonical Wnt signaling in the heart tissue. In order to investigate the cardiac function following MI in FZD1 pre-immunized mice, hemodynamic parameters were measured and improved cardiac systolic and diastolic function was observed. In addition, decreased myocyte cross-sectional area and increased pro-fibrotic genes were observed in FZD1 pre-immunized MI mice compared to control buffer injected MI group. These data indicated that FZD1 autoantibodies act as agonist to FZD1 receptors and induced activation of canonical

Wnt signaling in the heart tissue, which led to attenuated hypertrophy and enhanced fibrosis following MI, finally an improved heart function.

To gain more insight into the role of FZD1 and canonical Wnt signaling pathway in the wound healing process following MI, cardiac myocytes and fibroblasts were isolated respectively from neonatal rat hearts for further *in vitro* study. Hypoxic culture was used to mimic the pathological process of MI. In cardiac myocytes, FZD1 siRNA depletion decreased the canonical Wnt activity, which caused significantly increased myocyte size under hypoxia. In cardiac fibroblasts, FZD1 siRNA knockdown led to the downregulation of canonical Wnt activity as well, which finally resulted in reduced migration and differentiation of fibroblasts under hypoxia. These data demonstrated that downregulation of FZD1 caused enhanced hypertrophy and reduced fibrosis.

In summary, the present study suggests a new therapeutic method to potentially improve wound healing after MI through active immunization with FZD1 protein, and demonstrates a protective role of FZD1 through canonical Wnt pathway following cardiac injury.