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Inhibition of Wnt/β-catenin pathway promotes regenerative cardiac repair following myocardial infarct

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The Wnt/β-catenin pathway is temporarily activated in the heart following myocardial infarct. The effect of therapeutic inhibition of Wnt pathway on post injury outcome is unknown. Using a newly available, small molecule, GNF6231, which averts Wnt pathway activation by inhibiting Wnt secretion, we sought to investigate whether therapeutic inhibition of the Wnt pathway temporarily after infarct can mitigate post injury cardiac dysfunction and fibrosis, hence, reconciling discordant observations from genetic studies. Pharmacologic inhibition of the Wnt pathway by GNF-6231 significantly reduced the decline in cardiac function (ΔFractional Shortening%: 1.4±2.312 in GNF-6231 treated vs. -1.713±3.59 in vehicle-treated), prevented adverse cardiac remodeling and reduced infarct size (9.07±3.98% vs. 17.18±4.97%). Histologically, Wnt inhibition augmented proliferation of interstitial cells, particularly in the distal myocardium, inhibited cell death, including apoptosis of cardiomyocytes, and reduced myofibroblasts proliferation in the peri-infarct region. *In vitro* studies showed that Wnt inhibition increased proliferation of $Sca1^{+}$ cardiac progenitors, improved survival of cardiomyocytes and inhibited collagen I synthesis by cardiac myofibroblasts. Systemic and temporary pharmacologic inhibition of the Wnt pathway following MI resulted in improved function, reduced adverse remodeling and reduced infarct size in mice. Therapeutic Wnt inhibition affected multiple aspects of infarct repair: It promoted proliferation of cardiac progenitors and other interstitial cells, inhibited myofibroblasts proliferation, improved cardiomyocyte survival and reduced collagen I synthesis by myofibroblasts. Our data pointed to a promising role for Wnt inhibitory therapeutics as a new class of drugs to drive post MI repair and prevent heart failure.

Biography

Pampee P Young is a tenured Associate Professor in the Department of Pathology, Microbiology and Immunology at Vanderbilt University Medical Center. She completed her undergraduate degree at Rice University in Houston, Texas and obtained her MD/PhD degrees at UT Southwestern in Dallas, Texas. Her basic Science Research Program in Regenerative Medicine addresses the role of stem cells and our endogenous repair mechanisms to drive wound healing. Our work is funded by the Veterans Affairs, Pharmaceuticals and NIH. She also serves as the Medical Director of Transfusion Medicine and Stem Cell Laboratory at Vanderbilt University Hospital and the Veterans Affairs in Nashville.

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