RESEARCH ARTICLE SUMMARY

TISSUE REGENERATION

Inhibition of the prostaglandin-degrading enzyme 15-PGDH potentiates tissue regeneration

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INTRODUCTION: Agents that promote tissue regeneration could be beneficial in a variety of clinical settings, such as stimulating recovery of the hematopoietic system after bone marrow transplantation. Prostaglandin PGE2, a lipid signaling molecule that supports expansion of several types of tissue stem cells, is a candidate therapeutic target for promoting tissue regeneration in vivo. To date, therapeutic interventions have largely focused on targeting two PGE2 biosynthetic enzymes, cyclooxygenase-1 and cyclooxygenase-2 (COX-1 and COX-2), with the aim of reducing PGE2 production. In this study, we take the converse approach: We examine the role of a prostaglandin-degrading enzyme, 15-hydroxyprostaglandin dehydrogenase (15-PGDH), as a negative regulator of tissue repair, and we explore whether inhibition of this enzyme can potentiate tissue regeneration in mouse models.

RATIONALE: We used 15-PGDH knockout mice to elucidate the role of 15-PGDH in regulating tissue levels of PGE2 and tissue repair capacity in multiple organs. We then developed SW033291, a potent small-molecule inhibitor of 15-PGDH with activity in vivo. We used SW033291 to investigate the therapeutic potential of 15-PGDH inhibitors in tissue regeneration and to identify a 15-PGDH–regulated hematopoietic pathway within the bone marrow niche.

RESULTS: We found that in comparison with wild-type mice, 15-PGDH–deficient mice display a twofold increase in PGE2 levels across multiple tissues—including bone marrow, colon, and liver—and that they show increased fitness of these tissues in response to damage. The mutant mice also show enhanced hematopoietic capacity, with increased neutrophils, increased bone marrow SKL (Sca-1$^+$ C-kit$^+$ Lin$^-$) cells (enriched for stem cells), and greater capacity to generate erythroid and myeloid colonies in cell culture. The 15-PGDH–deficient mice respond to colon injury from dextran sulfate sodium (DSS) with a twofold increase in cell proliferation in colon crypts, which confers resistance to DSS-induced colitis. The mutant mice also respond to partial hepatectomy with a greater than twofold increase in hepatocyte proliferation, which leads to accelerated and more extensive liver regeneration. SW033291, a potent small-molecule inhibitor of 15-PGDH (inhibitor dissociation constant K_i ~0.1 nM), recapitulates in mice the phenotypes of 15-PGDH gene knockout, inducing increased hematopoiesis, resistance to DSS colitis, and more rapid liver regeneration after partial hepatectomy. Moreover, SW033291-treated mice show a 6-day-faster reconstitution of hematopoiesis after bone marrow transplantation, with accelerated recovery of neutrophils, platelets, and erythrocytes, and greater recovery of bone marrow SKL cells. This effect is mediated by bone marrow CD45$^-$ cells, which respond to increased PGE2 with a fourfold increase in production of CXCL12 and SCF, two cytokines that play key roles in hematopoietic stem cell homing and maintenance.

CONCLUSIONS: Studying mouse models, we have shown that 15-PGDH negatively regulates tissue regeneration and repair in the bone marrow, colon, and liver. Of most direct utility, our observations identify 15-PGDH as a therapeutic target and provide a chemical formulation, SW033291, that is an active 15-PGDH inhibitor in vivo and that potentiates repair in multiple tissues. SW033291 or related compounds may merit clinical investigation as a strategy to accelerate recovery after bone marrow transplantation and other tissue injuries. ■

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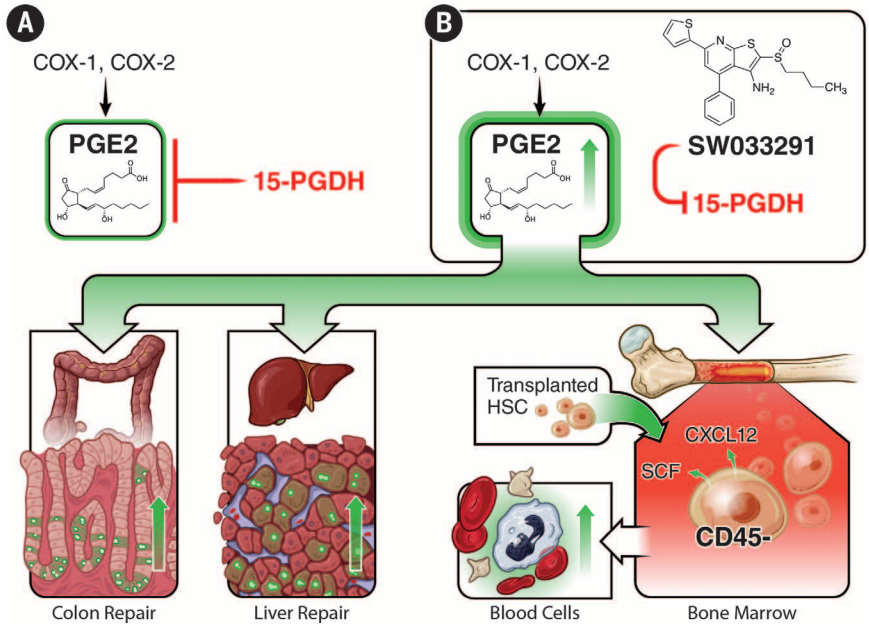

Inhibiting 15-PGDH accelerates tissue repair. (**A**) The enzyme 15-PGDH degrades and negatively regulates PGE2. (**B**) SW033291 inhibits 15-PGDH, increases tissue levels of PGE2, and induces CXCL12 and SCF expression from CD45$^-$ bone marrow cells. This in turn accelerates homing of transplanted hematopoietic stem cells (HSC), generation of mature blood elements, and post-transplant recovery of normal blood counts. Inhibiting 15-PGDH similarly stimulates cell proliferation after injury to colon or liver, accelerating repair of these tissues.

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