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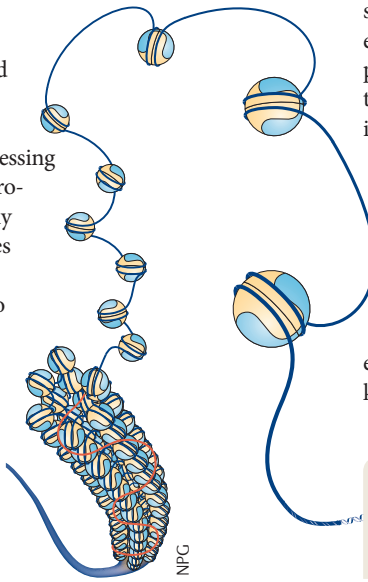
ANAEMIA

Targeting epigenetics in renal anaemia

Anaemia associated with chronic kidney disease results from impaired function of renal erythropoietin-producing cells (REPCs), leading to insufficient erythropoiesis. Now research suggests a mechanistic role for epigenetic changes in the reduced function of REPCs in fibrosis and demonstrates that targeting these changes can restore erythropoietin production and ameliorate anaemia in mice with fibrotic kidneys. "One of our most significant findings is that REPCs remain in fibrotic kidneys and that their ability to produce erythropoietin can be stimulated by demethylation treatment," says researcher Shuei-Liong Lin. "Moreover, demethylation treatment seems to redifferentiate myofibroblasts into pericyte-like cells."

Previous work by Lin and others had shown that although kidney pericytes are crucial for microvascular stability, they can differentiate into collagen-producing myofibroblasts. "We were curious to know whether normal kidney pericytes are REPCs and whether they lose erythropoietin-producing functionality in fibrotic kidneys," says Lin.

To investigate this possibility, the researchers created transgenic mice carrying a reporter in erythropoietin-producing and Col1a1-expressing cells. They found that erythropoietin expression drastically increased in kidney pericytes in response to phlebotomy-induced anaemia. Using two models of renal fibrosis, the researchers then showed that the transition of pericytes to myofibroblasts was associated with reduced erythropoietin production and a diminished ability of these cells to respond to anaemic stimuli.



To identify the mechanism by which erythropoietin production is impaired in fibrotic kidneys, Lin and colleagues assessed the methylation status of genomic DNA obtained from normal kidney pericytes and fibrotic kidney myofibroblasts. "After analyses of the extent of methylation in the 5′-untranslated region of the erythropoietin gene, we are sure that hypermethylation of the erythropoietin gene happens during pericyte-to-myofibroblast transition," explains Lin. Treatment of isolated myofibroblasts and fibrotic mice with non-toxic doses of the demethylating agent 5-azacytidine restored the basal expression and response of erythropoietin to hypoxia. "These findings demonstrate a role for hypermethylation in the repression of erythropoietin production in fibrotic kidneys," explains Lin.

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ORIGINAL ARTICLE(S) Chang, Y.-T. *et al.* DNA methyltransferase inhibition restores erythropoietin production in fibrotic murine kidneys. *J. Clin. Invest.* http://dx.doi.org/10.1172/JCI82819