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What's Past is Prologue: Developmental Pathways and Chronic Allograft Dysfunction

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Abstract

The authors discuss how understanding developmental signaling pathways that are reactivated in fibrotic kidney disease might lead to new therapeutic strategies for chronic allograft dysfunction.

A useful if simplistic way to view adult regeneration is through the lens of embryonic development. Injury to an adult organ often reactivates certain developmental signaling pathways that had been important during organogenesis. Some aspects of the tissue injury response recapitulate embryonic programs in a variety of solid organs including kidney (1). In the case of acute injury, these developmental signaling pathways regulate the generation and differentiation of new cells to replace injured ones, and the pathway then turns off after repair is complete. With chronic or repetitive injury, however, the prolonged activation of developmental pathways may be maladaptive, leading to depletion of regenerative capacity, loss of parenchyma and fibrosis. Understanding which developmental pathways regulate both repair and fibrosis may lead to novel therapeutic approaches to chronic disease.

Identifying the key signals in a disease like chronic allograft nephropathy (CAN) is complicated by its slow timecourse and the heterogeneity of insults that contribute to its pathogenesis (2). Despite these obstacles, improving long-term kidney transplant survival has become a major priority. One-year graft survival is now above 90% and yet the rate of allograft failure beyond that has remained constant (3,4). Characterized by interstitial fibrosis, tubular atrophy, vascular occlusive changes, glomerulosclerosis and progressive renal dysfunction, CAN is the leading cause of long-term kidney transplant failure. A detailed description of the most important signaling pathways and key cell types involved is needed, and should identify new diagnostic biomarkers and provide a roadmap for future therapeutic intervention.

In this issue, von Toerne and colleagues utilized gene microarray to identify new signaling pathways involved in CAN (3). Using a Fischer to Lewis rat model of CAN, they measured gene expression at baseline and three different timepoints over the course of disease. A notable strength of the study is the comparison to kidney gene expression in rats treated with retinoic acid – a metabolite of vitamin A that itself regulates development and is known to protect against adult kidney injury including models of CAN (4). By comparing gene expression in untreated to retinoid-treated rats, the authors were able to generate new hypotheses concerning the mechanisms by which retinoids mediate their protective effects. Retinoic acid is known to have pleiotropic effects including anti-inflammatory, anti-

proliferative and pro-differentiation, however the molecular mechanisms by which it ameliorates kidney injury is undefined.

Analysis of these datasets revealed upregulation of two important developmental signaling pathways, the Wnt and Hedgehog (Hh) pathways. The authors validated the relevance of these pathways by measuring multiple ligands as well as downstream target genes for each pathway. The integration of these gene changes across the whole pathway suggests true pathway activation, and is another strength of this work. They also documented or imply changes in localization of downstream effectors, by showing nuclear accumulation of β -catenin in the canonical Wnt pathway, and by demonstrating ciliary loss, which could influence down stream events in Hh or Wnt signaling.

The identification of Wnt and Hh pathways as potential new players in CAN is intriguing and fits with the concept that disease states may mimic development, since both of these pathways are critical for normal nephrogenesis (5). Wnt genes are increasingly recognized as master regulators of tissue repair, and in some cases their antagonism ameliorates chronic renal fibrosis (6). By contrast, almost nothing is known about the Hh pathway in adult kidney, and evaluating the functional role of this pathway in adult kidney injury will be an important challenge in the future.

This work points to several important lessons. First, gene microarray and newer technologies such as second-generation cDNA sequencing (RNAseq) will increasingly be used to uncover the mechanisms of therapy rather than to simply catalog genes whose expression changes over time in a disease model. This knowledge should help refine therapeutic strategies, for example by indicating combinations of drugs that target separate steps in the same pathway. Second, as with any gene array study, compiling the gene expression database is only the beginning. The authors have done an admirable job in validating the gene expression data, but an important limitation of the current study is that the gene changes measured reflect those of the whole kidney. Individual cellular responses cannot be identified by this approach, and indeed many will be lost amidst the whole-kidney transcriptome particularly for minority cell types. It will be critical to define Wnt and Hh ligand secreting and responding cells and to assess mechanistically how retinoic acid modulates their expression and downstream signaling. This information will help answer whether CAN truly recapitulates developmental paradigms or not. Irrespective of whether these results support the concept of injury as a recapitulation of development, the findings of von Toerne and colleagues implicate new pathways that could serve as potential targets for the next generation of CAN therapies.

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