BuMPy road of delayed graft function

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DELAYED GRAFT FUNCTION (DGF) occurs in 20–30% of renal transplants and contributes significantly to the gradual loss of grafts through accelerated development of chronic allograft dysfunction. Members of the transforming growth factor-β (TGF-β) family are incriminated as the major driving force for developing fibrosis. In an issue of the American Journal of Physiology—Renal Physiology, Simone and coworkers (7) present their findings that identify a novel pathway induced in postischemic kidneys with DGF and potentially leading to fibrosis. Specifically, these investigators discovered that a member of the TGF superfamily, bone morphogenetic protein-2 (BMP-2), becomes overexpressed in postischemic kidneys and renal allografts undergoing DGF. Receptors for BMP-2, ALK-2, -3, -6, and ACVR-2, are also expressed in the kidney, and, particularly, by the subset of CD133+/CD24- cells considered to represent adult renal progenitor cells (ARPC). Uprogelation of BMP-2 induces α-smooth muscle actin (α-SMA), collagen-1, and fibronectin synthesis in cultured ARPC, but not in epithelial cell lines, although these cells also express receptors for BMP-2. Similar myofibroblastic transition of CD133+ cells is detected in kidneys undergoing DGF, but not prior to it. The authors revealed that BMP-2 signaling in ARPC involves Nox4-mediated production of reactive oxygen species, which are mechanistically responsible for the myofibroblastic transition of the ARPC, and abrogating signaling by reactive oxygen species prevents the transition to a myofibroblastic phenotype. These findings hold the key to unlock doors to several intriguing and hitherto unresolved problems.

BMPs were initially identified as inducers of bone formation (9), and there are up to 20 members of this family (3). Multiple non-osteogenic functions of BMPs have been disclosed, such as development of the neural crest (BMP-2) or induction of a sympathetic adrenergic phenotype (BMP-4 and -7), whereas mutations in the BMP type II receptor have been linked to familial pulmonary arterial hypertension. BMP-2-deficient mice die on embryonic day 7.5 due to abnormal development of the heart, and proper BMP-2:BMP receptor type II signaling is believed to be important in cardiovascular morphogenesis (5). However, in adulthood, BMP-2 is considered mainly as an osteoinductive growth factor, and clinical trials utilizing a recombinant protein, rhBMP-2, established its efficacy in spinal fusion surgery, fracture healing, or bone formation around dental implants.

Unexpectedly, in diabetes and in atherosclerotic plaques, BMP-2 is upregulated and its signaling in the vasculature has been identified as a cause of calcification (2, 8), and now acute kidney injury and DGF have been added to this list (7). Induction of BMP-2 is achieved by high glucose levels, tumor necrosis factor-α, and reactive oxygen species, as aptly summarized elsewhere (6). In turn, BMP-2 upregulates Msx2 transcription factor and transcriptional regulator Runx2, which reprogram vascular adventitial cells to acquire an osteogenic or chondrogenic phenotype and, via the secreted Wnt signaling transmitted by blood flow through the vasa vasorum (it can be antagonized by the inhibitory ligand Dickkopf), deliver Wnt to the tunica media where it initiates concentric mineralization. Do similar events take place in DGF? It would be interesting to examine renal biopsies from patients with DGF for the signs of ectopic calcification and expression of Msx2 and Runx2.

Adventitial cells responding to BMP-2 signaling with osteogenic Msx2 expression are of particular interest. These cells have been identified as myofibroblasts related to microvascular pericytes, both descendants of the Scal+CD34+ mesenchymal progenitor, the mesangioblast (reviewed in Ref. 6). Whether ARPC, described by Simone et al. (7), are also the descendants of mesangioblasts or pericytes remains to be established. An alternative scenario for vascular calcification, which is highly relevant to kidney diseases, involves α-SMA+-vascular smooth muscle cells, which acquire an osteochondrogenic phenotype by upregulating the type III sodium-dependent phosphate cotransporter Pit-1 in response to BMP-2 and hyperphosphatemia (4). Senescent vascular smooth muscle cells have also been implicated in the process of vascular calcification due to the possible upregulation of BMP-2 and downregulation of its inhibitor, matrix Glα protein (1).

Finally, what could be the nature of BMP-2 upregulation in response to metabolic or ischemic stress? Is it a part of a default response, just as is the upregulation of TGF-β, and, if it is, what are the evolutionary benefits of such a response? Is the BMP-2 response to stress geared toward physical isolation of the injured tissue by “stonewalling” it from the surrounding intact parenchyma? Or are there other hitherto unknown functions of BMP-2? Resolution of these questions could be accomplished through the use of the known inhibitors of BMP-2 and studies of their outcomes. These include matrix Glα protein, which functions as a noggin-like inhibitor of BMP-2 signaling; inorganic pyrophosphate, which stabilizes the vascular smooth muscle cell phenotype; Dickkopf homologs, which antagonize osteogenic activity of Wnt signaling; inhibitors of Pit-1; fetuin, an inhibitor of calcification that controls the metabolism of vascular matrix vesicles; or activators of Smad6, which attenuates activation of BMP-2 signaling. Finding out how these molecules affect the course of DGF and its outcomes could be pathogenetically telling and potentially beneficial therapeutically.

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REFERENCES