PDGFR-β and kidney fibrosis

Alberto Ortiz

Chronic kidney disease (CKD) is one of the fastest growing global causes of death, estimated to rank among the top five by 2040 (Foreman et al., 2018). This illustrates current pitfalls in diagnosis and management of CKD. Advanced CKD requires renal function replacement by dialysis or transplantation. However, earlier CKD stages, even when renal function is still normal, are already associated with an increased risk of premature death (Perez-Gomez et al., 2019). Thus, novel approaches to diagnose and treat CKD are needed. The histopathological hallmark of CKD is kidney fibrosis, which is closely associated with local inflammation and loss of kidney parenchymal cells. Thus, kidney fibrosis is an attractive process to develop tests allowing an earlier diagnosis of CKD and represents a potential therapeutic target to slow CKD progression or promote regression.

From the therapeutic point of view, there is an ongoing discussion on the active contribution of fibrosis to CKD progression, and thus, on whether targeting fibrosis may effectively slow or even reverse CKD; or on the contrary, if fibrosis represents a common end-stage of any CKD, its targeting would not alter the natural history of CKD. Finally, fibrosis may even be a healing, beneficial process (Djudjaj & Boor, 2019). Clinical evidence on the active role of fibrosis allows several interpretations. On one hand, clinical trials exploring approaches directly targeting fibrosis have so far failed (Ramos et al., 2020). On the other hand, renin–angiotensin system (RAS) blockade, which constitutes the best established nephroprotective strategy, interferes with fibrosis along with other pathogenic processes.

In the present issue of EMBO Molecular Medicine, Buhl et al. (2020) conclusively demonstrate that deregulated hyperactivity of the platelet-derived growth factor receptor-β (PDGFR-β) in mouse renal mesenchymal cells leads to pathological proliferation of mesangial cells and interstitial fibroblasts. It further leads to a phenotype switch toward myofibroblasts driving mesangial sclerosis, interstitial fibrosis, decreased GFR, and renal anemia (Buhl et al., 2020). In short, PDGFR-β overactivity in renal mesenchymal cells caused CKD. This preclinical model is clinically relevant since increased expression of PDGFR-β by kidney mesenchymal cells is found in human CKD, and the features of this murine model overlap with those of human CKD. PDGFR-β forms homodimeric or heterodimeric receptors for PDGF-B and PDGF-D, and targeting either PDGFR-β, PDGF-B, or PDGF-D has been protective in diverse preclinical models of kidney disease. The originality of the present study is fourfold:

First, hyperactivity of a single receptor in mesenchymal cells only drove glomerular and interstitial fibrosis, and this preceded tubular atrophy and interstitial inflammation in the absence of hypertension, albuminuria or hematuria (Fig 1). Thus, the study demonstrates that fibrosis itself is pathogenic and may drive the full spectrum of CKD even in the absence of primary insult to parenchymal kidney cells or without engagement of common drivers of clinical CKD progression (proteinuria, hematuria, hypertension).

Second, PDGFR-β hyperactivity committed erythropoietin (EPO)-producing interstitial cells to a fibrogenic phenotype at the expense of EPO production, thus driving anemia. This identifies PDGFR-β as a negative regulator of physiological endocrine kidney EPO, which differs from the tumor microenvironment situation, where PDGF-BB signaling via PDGFR-β in local stromal cells induces EPO production. This may promote tumor growth through paracrine stimulation of tumor angiogenesis and by endocrine stimulation of extramedullary hematopoiesis (Xue et al., 2011). This finding opens the door to adjunctive therapies for uremic anemia that target PDGFR-β hyperactivity in diseased kidneys. In this regard, it is significant that imatinib, an...
inhibitor of multiple receptor kinases, including PDGFR-β, reversed anemia in mice with mesenchymal cell PDGFR-β hyperactivity (Buhl et al., 2020). Indeed, anemia is a common adverse effect of imatinib used for cancer treatment.

Third, myofibroblast cell number and interstitial fibrosis (but not glomerular sclerosis) abnormalities were reversed by imatinib. However, whether there is an immediate clinical translation of this observation remains to be demonstrated. Indeed, the impact of imatinib on GFR was not addressed, and therapeutic use for human disease may be limited by the lack of impact on glomerular fibrosis, since glomerular health is a key determinant of GFR. Additionally, at the doses currently used in human cancer, imatinib has been associated with an increased incidence of acute kidney injury and chronic loss of GFR. Further research is thus warranted to define potentially nephroprotective imatinib regimens or to identify the specific additional kinases targeted by imatinib that may preclude nephroprotection in humans. While PDGFR-β targeting with current tools may have limitations, Buhl et al identified the early signaling pathways engaged by PDGFR-β overactivity in mesenchymal kidney cells. Interferon-related signaling and JAK/STAT signaling were prominently represented. However, JAK/STAT signaling was not involved in kidney fibrosis in this model. This is important information since the JAK/STAT inhibitor baricitinib decreased albuminuria in diabetic kidney disease trials, although clinical development appears to have stalled.

Finally, a pure kidney fibrosis model may help set up kidney imaging or proteomics/molecular imaging of kidney fibrosis in vivo. Kidney Int 97: 609–614

Buhl EM, Djudjaj S, Klinkhammer BM, Ermert K, Puelles VG, Lindenmeyer MT, Cohen CD, He C, Borkham-Kamphorst E, Weiskirchen R et al (2020) Dysregulated mesenchymal PDGFR-β drives kidney fibrosis. EMBO Mol Med 12: e11021

Djudjaj S, Boor P (2019) Cellular and molecular mechanisms of kidney fibrosis. Mol Aspects Med 65: 16–36

Foreman KJ, Marquez N, Dolgert A, Fukutake K, Fullnam N, McCaughey M, Pletcher MA, Smith AE, Tang K, Yuan CW et al (2018) Forecasting life expectancy, years of life lost, and all-cause and cause-specific mortality for 250 causes of death: reference and alternative scenarios for 2016–40 for 195 countries and territories. Lancet 392: 2052 – 2090

González-Rinne A, Luis-Lima S, Escamilla B, Negrín-Mena N, Ramírez A, Morales A, Vega N, García P, Cabello E, Marrero-Miranda D et al (2019) Impact of errors of creatinine and cystatin C equations in the selection of living kidney donors. Clin Kidney J 12: 748 – 755

References

Baues M, Klinkhammer BM, Ehling J, Gremse F, van Zandvoort MA, Reutelingsperger CPM, Daniel C, Amann K, Babičková J, Kiessling F et al (2019) A collagen-binding protein enables molecular imaging of kidney fibrosis in vivo. Kidney Int 97: 609–614

Buhl EM, Djudjaj S, Klinkhammer BM, Ermert K, Puelles VG, Lindenmeyer MT, Cohen CD, He C, Borkham-Kamphorst E, Weiskirchen R et al (2020) Dysregulated mesenchymal PDGFR-β drives kidney fibrosis. EMBO Mol Med 12: e11021

Djudjaj S, Boor P (2019) Cellular and molecular mechanisms of kidney fibrosis. Mol Aspects Med 65: 16–36

Foreman KJ, Marquez N, Dolgert A, Fukutake K, Fullnam N, McCaughey M, Pletcher MA, Smith AE, Tang K, Yuan CW et al (2018) Forecasting life expectancy, years of life lost, and all-cause and cause-specific mortality for 250 causes of death: reference and alternative scenarios for 2016–40 for 195 countries and territories. Lancet 392: 2052 – 2090

González-Rinne A, Luis-Lima S, Escamilla B, Negrín-Mena N, Ramírez A, Morales A, Vega N, García P, Cabello E, Marrero-Miranda D et al (2019) Impact of errors of creatinine and cystatin C equations in the selection of living kidney donors. Clin Kidney J 12: 748 – 755

References

Baues M, Klinkhammer BM, Ehling J, Gremse F, van Zandvoort MA, Reutelingsperger CPM, Daniel C, Amann K, Babičková J, Kiessling F et al (2019) A collagen-binding protein enables molecular imaging of kidney fibrosis in vivo. Kidney Int 97: 609–614

Buhl EM, Djudjaj S, Klinkhammer BM, Ermert K, Puelles VG, Lindenmeyer MT, Cohen CD, He C, Borkham-Kamphorst E, Weiskirchen R et al (2020) Dysregulated mesenchymal PDGFR-β drives kidney fibrosis. EMBO Mol Med 12: e11021

Djudjaj S, Boor P (2019) Cellular and molecular mechanisms of kidney fibrosis. Mol Aspects Med 65: 16–36

Foreman KJ, Marquez N, Dolgert A, Fukutake K, Fullnam N, McCaughey M, Pletcher MA, Smith AE, Tang K, Yuan CW et al (2018) Forecasting life expectancy, years of life lost, and all-cause and cause-specific mortality for 250 causes of death: reference and alternative scenarios for 2016–40 for 195 countries and territories. Lancet 392: 2052 – 2090

González-Rinne A, Luis-Lima S, Escamilla B, Negrín-Mena N, Ramírez A, Morales A, Vega N, García P, Cabello E, Marrero-Miranda D et al (2019) Impact of errors of creatinine and cystatin C equations in the selection of living kidney donors. Clin Kidney J 12: 748 – 755
Magalhães P, Pejchinovski M, Markoska K, Banasik M, Klinger M, Švec-Bilá D, Rychlík I, Ratto M, Restivo A, Capasso G et al (2017) Association of kidney fibrosis with urinary peptides: a path towards non-invasive liquid biopsies? Sci Rep 7: 16915

Perez-Gomez MV, Bartsch LA, Castillo-Rodriguez E, Fernandez-Prado R, Fernandez-Fernandez B, Martin-Cleary C, Gracia-Iguacel C, Ortiz A (2019) Clarifying the concept of chronic kidney disease for non-nephrologists. Clin Kidney J 12: 258 – 261

Ramos AM, Fernández-Fernández B, Pérez-Gómez MV, Carriazo Julio SM, Sanchez-Niño MD, Sanz A, Ruiz-Ortega M, Ortiz A (2020) Design and optimization strategies for the development of new drugs that treat chronic kidney disease. Expert Opin Drug Discov 15: 101 – 115

Selby NM, Blankestijn PJ, Boor P, Combe C, Eckardt KU, Eikefjord E, García-Fernandez N, Golay X, Gordon I, Grenier N et al (2018) Magnetic resonance imaging biomarkers for chronic kidney disease: a position paper from the European COST Action PARENCHIMA. Nephrol Dial Transplant 33(Suppl 2): ii4 – ii14

Xue Y, Lim S, Yang Y, Wang Z, Jensen LD, Hedlund EM, Andersson P, Sasahara M, Larsson O, Galter D et al (2011) PDGF-BB modulates hematopoiesis and tumor angiogenesis by inducing erythropoietin production in stromal cells. Nat Med 18: 100 – 110

License: This is an open access article under the terms of the Creative Commons Attribution 4.0 License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.