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JAK3 talks down to renal 25-hydroxyvitamin D 1 α -hydroxylase

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25-Hydroxyvitamin D 1 α -hydroxylase CYP27B1 is expressed in several extrarenal tissues. In the immune system, and likely elsewhere, its expression is not regulated by calcium and phosphate homeostatic inputs. Umbach *et al.* provide evidence that inflammatory cytokine signaling may also control CYP27B1 expression in renal epithelia. Mice lacking JAK3, a kinase essential for immune homeostasis, displayed mild renal inflammation, elevated renal CYP27B1 expression, and altered phosphate metabolism, linking immune signaling to vitamin D metabolism in the kidney.

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The vitamin D field has undergone somewhat of a paradigm shift in the past few years. In the classic model of vitamin D metabolism, circulating 25-hydroxyvitamin D produced largely and constitutively in the liver is 1 α -hydroxylated to produce hormonal 1,25-dihydroxyvitamin D (1,25(OH)₂D) by the action of renal CYP27B1 and released into the circulation in addition to acting locally. CYP27B1 expression in the kidneys is controlled by calcium and phosphate homeostatic inputs, consistent with the predominant role of vitamin D signaling in calcium and phosphate homeostasis; renal 1,25(OH)₂D synthesis is induced by parathyroid hormone under conditions of reduced circulating Ca²⁺, and jointly inhibited by Klotho and by FGF23 released from bone in a negative-feedback loop.^{1,2} However, the

relative simplicity of this view has been challenged on a number of fronts. First, the vitamin D receptor (VDR), a member of the nuclear receptor family of hormone-regulated transcription factors, is expressed in a vast array of tissues, most of which are not implicated in calcium and phosphate homeostasis. Notably, the VDR is widely expressed in the immune system.³ Moreover, a landmark study by Hewison and colleagues⁴ as well as several subsequent papers showed that CYP27B1 is also present in a large number of extrarenal tissues. Collectively, these results potentially link vitamin D metabolism and signaling to multiple physiological responses distinct from calcium homeostasis.

To fully understand the scope of the actions of vitamin D, the field needs to determine the signaling pathways regulating extrarenal CYP27B1 expression, as these would provide critical clues to the physiological responses regulated by 1,25(OH)₂D signaling in peripheral tissues. To date, studies in the immune system have served as an excellent model in this regard. Several groups have shown that vitamin D signaling regulates both the innate and adaptive

arms of the immune system. For example, 1,25(OH)₂D regulates several aspects of T-cell biology.⁵ In addition, the VDR induces the expression of several genes encoding multiple elements of innate immune responses, including antimicrobial peptides, pattern recognition receptors, and cytokines, among others.³ More importantly, 1 α -hydroxylase expression is induced by several immune signaling pathways in macrophages and other immune cell types. Stimulatory signals include a complex array of cytokines, including interferon- γ (IFN- γ), as well as pathogen recognition by toll-like receptors.³ Thus, the immune system is wired to produce 1,25(OH)₂D locally in response to infection.

The work of Umbach *et al.*⁶ (this issue) has now revealed potential links between immune system regulation of CYP27B1 and its expression in the kidney. They were interested in studying the potential role of signaling through Janus kinase 3 (JAK3) in controlling CYP27B1 expression. JAK3 is one of the Janus kinases that lie downstream of cytokine receptor signaling (the others being JAK1, JAK2, and TYK2). Of the four, it is the most tissue-restricted in expression, and it is considered to be largely lymphoid-specific.⁷ However, several studies have shown that JAK3 is also expressed in epithelial cells, including those in the kidney.⁸ Biochemical and genetic experiments have revealed that JAK3 binds to the common γ -chain (γ_c), which is a component of receptors of the members of the lymphoid-predominant interleukin-2 (IL-2) cytokine family (for example, receptors for IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21; Figure 1). Consistent with this, Jak3 and γ_c knockout mice, as well as humans lacking JAK3, exhibit severe combined immunodeficiency (SCID)-like defects.⁷ Umbach *et al.*⁶ link JAK3 to IFN- γ signaling, a previously characterized inducer of CYP27B1 gene expression. While JAK3 is not directly associated with IFN receptors (unlike JAK1 and JAK2), it is activated by CD40 signaling (Figure 1), whose expression and function is tightly linked to IFN- γ .

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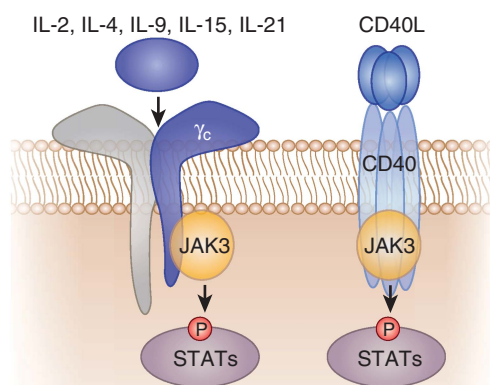


Figure 1 | JAK3 signaling lies downstream of IL-2 family receptors and CD40.

The most striking finding of the study by Umbach *et al.*⁶ is the renal phenotype of the *jak^{-/-}* mice. Histomorphological analysis of the kidneys revealed mesangial matrix expansion and mild glomerulosclerosis in *jak3*-null as compared with wild-type mice, which was attributed at least in part to elevated circulating levels of the inflammatory cytokine IL-12 observed in the knockout animals. More intriguing were the alterations in mineral ion homeostasis observed in the absence of JAK3. While circulating levels of calcium and phosphate were not affected by *jak3* disruption, fecal phosphate levels were reduced in the null mice, consistent with elevated intestinal phosphate absorption, whereas absolute and fractional renal phosphate excretion was significantly increased. *In vitro* experiments reported in the paper suggested that intracellular JAK3 signaling may influence the activity of coexpressed Napi-IIa, the major renal phosphate transporter. In addition, *jak3* disruption altered levels of calcium homeostatic hormones, most noticeably leading to an increase in circulating 1,25(OH)₂D and FGF23, as well as a trend toward reduced parathyroid hormone (PTH). Importantly, the increase in 1,25(OH)₂D could be attributed to substantially enhanced expression of renal CYP27B1, which is

particularly noteworthy under conditions of elevated FGF23 and reduced PTH concentrations. This effect appeared to be at least partially specific for the kidney, as no significant changes in intestinal CYP27B1 levels were observed.

The enhanced production of renal 1,25(OH)₂D on a *jak3*-null background is both intriguing and paradoxical. The authors suggest that the increase in CYP27B1 expression could be due at least in part to the elevated IL-12 levels observed in the null animals. IL-12 is known to increase expression of the transcription factor interferon regulatory factor-1 (IRF-1), and IRF-1 mRNA and protein were much higher in the kidneys of knockout animals compared with their wild-type counterparts. Furthermore, IRF-1 colocalized with CYP27B1 in glomerular parietal epithelium, proximal tubule, and collecting duct cells. IRF-1 expression was also stronger in adjacent interstitial cells, which were possibly of T-cell or myeloid origin. While these results are striking, it is not clear whether the proposed effect of IL-12 on IRF-1 expression would be direct or indirect, as signaling of IL-12 in renal epithelial cells has yet to be demonstrated. Moreover, the elevated expression of CYP27B1 in the absence of JAK3 might appear somewhat paradoxical, as JAK3

is activated downstream of IL-15 signaling, an inducer of *CYP27B1* gene expression. In addition, other work has shown that JAK3 activation correlates with elevated IRF-1 expression, at least in B cells.⁹ One might have thus predicted the opposite effect of *jak3* ablation on renal CYP27B1 expression. Nonetheless, the study by Umbach *et al.*⁶ represents an important contribution as it reveals that the signaling pathways controlling renal CYP27B1 expression are more complex than previously appreciated, and it suggests that immune-regulatory inputs can control epithelial vitamin D metabolism in the kidney. It will be of considerable interest to determine the signaling pathways that directly control the elevated renal CYP27B1 expression observed in the knockout animals.

DISCLOSURE

The author declared no competing interests.

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