potassium have also been shown in patients with MSK, potentially contributing to the pathogenesis of nephrolithiasis.3

This renal malformation is frequently associated with nephrocalcinosis and renal stones. In particular, MSK is associated with a 60% lifetime risk of renal stones, and the prevalence of MSK in patients with renal stones is significantly higher (8.5%, \(P < 0.01\)) than in the control population (1.5%).4

As MSK was diagnosed only after the introduction of intravenous urography in the 1930s (Figure 1), and conventional computed tomography, which has been preferred since the mid-1990s, is not satisfactory for unmasking MSK, except when using multidetector-row computed tomography of high-resolution three-dimensional displays and late urographic images, ‘there is a concrete possibility of this renal condition being forgotten in the future.’5 Therefore, it seems to be even more mandatory not to miss MSK in reviews of renal stones.


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Response to ‘The missing medullary sponge kidney’
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I agree with Stratta et al.1 that the association of various malformative disorders with medullary sponge kidney (MSK) is interesting, yet challenging. These various associations have led to the hypothesis that embryological nephronal maldevelopment may participate in the pathogenesis of this disease.2 However, as stated in a very recent article published in this journal, the pathogenesis of MSK has not yet been fully elucidated.3 Although multiple candidate genes have been proposed to play a role in the process of embryological development, none have been revealed to be directly involved in uterine-bud/metanephric blastema interface disruption.3–5 This notion is supported by a study on the kidneys of pre-term infants showing an abundance of calcification-promoting molecules, specifically osteopontin and hyaluronan, expressed at the luminal side of the renal tubular differentiating cells.6

There was no mention made of the role of MSK in my recent paper7 because the true advancement in this field needs to be substantiated. This could be achieved by direct tissue examination of the renal papillary structure in affected patients for both the presence of undifferentiated embryonal tissue and for the expression of various potential genes participating in nephronal development. The metabolic abnormalities that were mentioned by Stratta et al.1 are only associations that may contribute to kidney stone formation but are not causal in the pathogenesis of this disease.8


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It takes two to Twist

To the Editor: It is with interest that we read the report of Sun et al.1 on how hypoxia-inducible factor-1α (HIF-1α) induces TWIST1 expression in human tubule cell lines, providing a model for hypoxia-induced renal fibrosis. Their findings complement two earlier papers linking hypoxic signaling to TWIST1 expression. In a functional screen in Caenorhabditis elegans, TWIST1 was identified as a HIF target, and in human cancer cells, hypoxia induces TWIST1 expression and epithelial-mesenchymal transition.2–4 Importantly, silencing of TWIST1 attenuates metastatic cancer outgrowth in xenograft models.4 Taken together, these
earlier studies had already established an important role for hypoxia-induced TWIST1 expression.

Whereas both Yang et al. and Sun et al. observe a role for HIF-1α in regulating TWIST1 through hypoxia-responsive elements in the TWIST1 proximal promoter, we showed a regulation of TWIST1 by HIF-2, the HIF-1 ortholog. Importantly, HIF-2α induces TWIST1 expression using a distinct intrinsic hypoxia-responsive element rather than through the proximal TWIST1 promoter. Although we excluded an involvement of HIF-1 in both intronic and proximal hypoxia-responsive element regulation of TWIST1, other studies have not addressed a role for HIF-2.

Therefore, it seems that hypoxic TWIST1 induction is regulated by both HIF-1α and HIF-2α proteins through distinct regulatory elements in a tissue-specific manner (Figure 1). It is clear that the hypoxic regulation of TWIST1 plays a key role in hypoxic epithelial–mesenchymal transition induction and metastases formation. It will be interesting to learn the mechanistic and clinical importance of the HIF-1α versus the HIF-2α-mediated regulation of TWIST1 in disease processes.

Reference:

Response to ‘It takes two to Twist’

We thank Vooijs et al. for their interest and comments about our paper. Vooijs et al. had found that hypoxia induces Twist1 expression in a hypoxia-inducible factor (HIF)-2α-dependent manner and that intrinsic hypoxia response elements of Twist1 are regulated by HIF-2α. In our study, direct transcriptional activation of Twist by HIF-1α was found to promote epithelial-to-mesenchymal transition (EMT) in tubular cells. Yang et al. also showed that HIF-1α directly regulates the expression of Twist by binding to hypoxia-responsive elements in the Twist proximal promoter, resulting in EMT and metastatic phenotypes. Thus, Twist may be the target gene of both HIF-1α and HIF-2α. However, we think the role of Twist in hypoxia-induced renal EMT and fibrosis is mediated only by HIF-1α, not HIF-2α.

The expressions of both HIF-1α and HIF-2α are tissue- and cell type-specific. HIF-1α is ubiquitously expressed, whereas HIF-2α expression is more restricted. HIF-2α has been found in hepatocytes, cardiomyocytes, glial cells, type II pneumocytes, and endothelial cells. In addition, it has been reported that HIF-1α and -2α are also expressed in different renal cell populations. HIF-1α is mainly induced in tubular cells as well as in proximal tubules, distal tubules, and connecting tubes. Although HIF-2α is not expressed in tubular cells, it is expressed in the endothelial cells of a small subset of glomeruli and in peritubular endothelial cells and fibroblasts. The selective induction of HIF-1α and -2α in different types of cells in the kidney should use different aspects of hypoxic response pathways in a cell type-specific or temporospatial manner. It would be interesting to further investigate the potential roles of the HIF-2α in hypoxic kidney.

In conclusion, although hypoxic Twist induction is regulated by both HIF-1α and HIF-2α in some specific cell types, including cancer cells, we feel that Twist-induced renal EMT and fibrosis under hypoxia are dominantly mediated by an HIF-1α-dependent pathway.


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