The essential role of BMP6 in hepcidin regulation

Hepcidin, a small peptide produced primarily by hepatocytes, plays a major role in the regulation of iron metabolism. It interacts with the cellular iron exporter ferroportin, causing its degradation and preventing release of iron from macrophages or intestinal cells into the plasma (1). The consequent increase in splenic iron and decrease in dietary iron absorption lead to decreased circulating iron levels. As expected, a feedback relationship exists between body iron status and hepcidin expression: hepcidin is upregulated in response to iron loading and decreased in response to iron deficiency.

Interestingly, hepcidin production is regulated by the BMP signaling pathway (2). BMPs are members of the TGF-β superfamily of ligands and initiate an intracellular signaling cascade by binding to two type I and two type II serine-threonine kinase receptors. The activated receptor complex phosphorylates cytoplasmic effectors, the Smad1, 5 and 8 proteins, which then form heteromeric complexes with Smad4 and translocate to the nucleus to modulate gene expression. Mutations in the BMP coreceptor, hemojuelin, are associated with inappropriately low hepcidin expression and massive iron overload in both humans and mice (3, 4). Suppression of hepatic BMP signaling by a liver-specific conditional knockout of Smad4 has similar consequences (5). BMP signaling can be inhibited in vivo with soluble hemojuelin which binds to endogenously secreted BMP ligands and prevents their interaction with cell surface receptors (6), or with dorsomorphin which blocks the ability of activated BMP type I receptors to phosphorylate Smad1/5/8 (7). The inhibition of BMP signaling reduces hepcidin expression and increases serum iron. Conversely, BMP administration in vivo increases hepcidin expression and reduces serum iron. In vitro, numerous BMP ligands, including BMP2, BMP4, BMP5, BMP6, BMP7 and BMP9, can regulate hepcidin when added exogenously. However, the observations made in cell culture do not always translate to the situation in vivo and, until last year, the exact nature of the endogenous ligand that activates the BMP/SMAD signaling cascade in response to iron was unknown.

We first observed that a systemic iron challenge induces hepatic Smad1/5/8 phosphorylation, which indicates that BMP signaling is involved in the feedback regulation of hepcidin transcription by iron. The analysis of the liver transcriptomes of mice kept on a low- or high-iron diet then showed that the levels of Bmp6 mRNA, but not that of other Bmps, were concordant with changes in hepcidin mRNA concentrations, suggesting that BMP6 could be the endogenous regulator of iron metabolism (8). Our group and that of J. Babitt recently confirmed this possibility. Indeed, targeted disruption of Bmp6 in mice causes a rapid and massive iron accumulation in the liver, pancreas, heart and kidney. Despite their severe iron overload, these mice have low levels of hepatic Smad1/5/8 phosphorylation and markedly reduced hepcidin synthesis, indicating that BMP6 is critical for iron homeostasis and functionally nonredundant with other members of the BMP subfamily of ligands (9, 10).

Impaired regulation of hepcidin expression in response to iron loading appears to be the pathogenic mechanism for hereditary hemochromatosis. The molecular function of the HFE
protein, involved in the most common form of hereditary hemochromatosis, is still unknown. We have used Hfe-deficient mice to test whether HFE has a role in the signaling cascade induced by BMP6. At weaning, these mice have normal Bmp6 mRNA levels, but inappropriately low hepcidin mRNA. This leads to increased iron absorption, progressive accumulation of iron in the liver and, as expected, increased Bmp6 mRNA and protein. However, this is followed by only a slight increase in hepcidin mRNA, insufficient in regard to the levels of Bmp6. Lack of HFE therefore impairs signal transduction induced by the BMP6 ligand (11).

Potential of BMP6 agonists and antagonists for the treatment of genetic hemochromatosis or iron-refractory iron deficiency anemia will be discussed at the workshop.

References