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## Podium #16

**AN ESSENTIAL ROLE FOR THE BMP-SMAD PATHWAY IN HEPCIDIN INDUCTION DURING ER STRESS AND NAFLD/NASH**

*Audrey Belot, PhD student<sup>2</sup>, Ophélie Goubeyre, Aude Rubio, Céline Besson-Fournier, Chloé Latour, Inka Gallitz, Alexandra Montagner, Arnaud Polizzi, Marion Régnier, Andrea U Steinbicker, Hervé Guillou, Marie-Paule Roth, Héléne Coppin and Delphine Meynard, PhD<sup>1</sup>*

*<sup>1</sup>INSERM; <sup>2</sup>IRSD, Université de Toulouse, INSERM, INRA, ENVT, UPS, France*

Presented By: Delphine Meynard, PhD

There is mounting evidence that both endoplasmic reticulum (ER) stress and hepatic iron deposition contribute to nonalcoholic steatohepatitis (NASH). Interestingly, ER stress is known to upregulate hepcidin, which could prevent iron efflux from macrophages and hepatocytes and cause hepatic iron deposition. The objective of this study was to characterize *in vivo* the mechanisms responsible for increased hepcidin expression during ER stress and NASH. To address this question, ER stress was induced in mice with tunicamycin (Tm). In wild-type mice (WT), Tm injection triggers ER-stress in the liver and leads to an increase in hepcidin mRNA expression. Crebh, a liver-specific transcription factor, was previously suggested to play an essential role in hepcidin regulation in response to ER stress. However, in our hands, hepcidin mRNA was increased to similar levels in Tm-injected Crebh<sup>-/-</sup> and wild-type (WT) mice, which seriously questions this hypothesis. Rather, we observed a rise in Smad5 phosphorylation and in Id1 mRNA expression in the liver in Tm-injected mice, indicating that Bmp-Smad signaling is activated in response to ER stress. An essential role for this pathway was provided using Bmpr1a<sup>-/-</sup> mice. Indeed, lack of Bmpr1a, the BMP type I receptor Alk3, prevents the induction of hepcidin mRNA expression in response to Tm treatment. To find out what activates Bmp-Smad signaling in ER stress, we examined mRNA expression of the different ligands of the TGF $\beta$ /BMP family. However, none of these ligands was induced in response to ER stress. Notably, activin B-deficient mice injected with Tm induce hepcidin as much as do WT mice, which eliminates the possibility that activin B plays a role in ER stress. BMP-Smad signaling in ER stress could also be activated independently of the induction of a ligand. Interestingly, we found a dramatic repression of Tmprss6 gene expression in Tm-injected mice, which very likely explains the increase in Smad5 phosphorylation and the induction of Id1 and hepcidin mRNA expression seen in these mice. To determine whether a similar mechanism explains the induction of hepcidin during NASH, we fed WT mice with a Methionine Choline Deficient (MCD) diet for 10 and 24 days. As expected, MCD diet leads to accumulation of lipid droplets and inflammatory foci in the liver of these mice, and to ER stress, as shown by the induction of eif2 $\alpha$  phosphorylation. Importantly, MCD diet also stimulates hepcidin mRNA expression and promotes liver iron deposition in hepatocytes and Kupffer cells. Remarkably, hepcidin upregulation in these mice coincides with an increase in Smad5 phosphorylation, an induction of Id1 and a repression of Tmprss6 expression, which suggests that the molecular mechanism of hepcidin upregulation in NASH is similar to the mechanism highlighted previously in Tm-injected mice and very likely reflects ER stress caused by lipid accumulation. Altogether, this study shows that hepcidin up-regulation in response to ER stress and NAFLD/NASH is promoted by the activation of Bmp-Smad signaling. Inhibiting the BMP-SMAD pathway could be a promising therapeutic option for NASH patients to reduce hepcidin expression, avoid liver iron deposition and thus prevent disease progression.