BK21 Plus Seminar

"Pharmacological treatment of nonalcoholic steatohepatitis by interleukin-22"

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- **Date: 2:00PM/Dec. 11(Wed.)/2019**
- **Place: Conference room(#179), PostechBiotech Center**
- **Inquiry: Prof. Sung Ho Ryu (279-2292)**
- **Abstract:**

Nonalcoholic fatty liver disease (NAFLD) is a spectrum of disease that ranges from fatty liver to nonalcoholic steatohepatitis (NASH), cirrhosis, and hepatocellular carcinoma and is a leading cause of chronic liver disease worldwide. While fatty liver is mostly devoid of inflammation and is considered benign, 10-20% of patients with fatty livers progress to NASH, which is characterized by the presence of hepatocyte injury, inflammation, and fibrosis. The pathogenic mechanisms of NASH involve molecular pathways that regulate lipid and glucose homeostasis, oxidative stress and mitochondrial targets in hepatocytes, inflammatory signals that converge on hepatocytes, and inflammatory signals and intracellular targets related to stellate cell activation and fibrogenesis. These mechanisms will be further discussed in the presentation with an overview of the investigational drugs that target these pathways.

A dominant feature of the inflammation observed in human NASH is a robust infiltration of neutrophils in the liver, which is not significantly observed in fatty livers in obese individuals or in high-fat diet (HFD)-fed mice. Hepatic expression of C-X-C motif chemokine ligand 1 (CXCL1), a key chemokine for neutrophil infiltration, is highly elevated in NASH patients but not in fatty livers in obese individuals or in HFD-fed mice. Our recent work demonstrated that overexpression of Cxcl1 in the liver promotes steatosis-to-NASH progression in HFD-fed mice by inducing neutrophil infiltration, oxidative stress, and stress kinase activation. Myeloid cell-specific deletion of the neutrophil cytosolic factor 1 (Ncf1)/p47phox gene, which contributes to neutrophil oxidative burst, markedly reduced CXCL1-induced NASH and stress kinase activation in HFD-fed mice. Treatment with interleukin (IL)-22 ameliorated CXCL1/HFD-induced NASH or methionine-choline deficient diet (MCD)-induced NASH in mice. Mechanistically, IL-22 blocked hepatic oxidative stress and its associated stress kinases via the induction of metallothionein, one of the most potent antioxidant proteins. Moreover, although it does not target immune cells, IL-22 treatment attenuated the inflammatory functions of hepatocyte-derived mitochondrial DNA-enriched extracellular vesicles, thereby suppressing liver inflammation in NASH. Overall, hepatic overexpression of CXCL1 is sufficient to drive steatosis-to-NASH progression in HFD-fed mice through neutrophil-derived reactive oxygen species and activation of stress kinases, which can be reversed by IL-22 treatment via the induction of metallothionein.

***This seminar will be given in English.**

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