Parenchymal-stromal Cell Interaction in Metabolic Diseases

Yoshihiro Ogawa MD, PhD

Department of Molecular Endocrinology and Metabolism, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University; JST, CREST

Chronic inflammation may involve sustained interaction between parenchymal and stromal cells in response to a variety of cellular stresses, thereby leading to tissue remodeling and organ malfunction. In obese adipose tissue, saturated fatty acids, which are released as a danger signal from hypertrophied adipocytes, stimulates a pathogen sensor TLR4 in the infiltrating macrophages, thus establishing a vicious cycle that aggravates inflammatory responses. Histologically, macrophages aggregate to constitute crown-like structures (CLS), where they are considered to scavenge the residual lipid droplets of dead adipocytes. Macrophage-inducible C-type lectin (Mincle), a pathogen sensor for *Mycobacterium tuberculosis*, is induced in adipose tissue macrophages constituting CLS, the number of which is correlated with the extent of interstitial fibrosis. Our data suggest that Mincle, when activated by an as-yet-unidentified danger signal released from dead or dying adipocytes, plays a key role in adipose tissue inflammation and fibrosis.

Free fatty acids, when released from the obese visceral fat depots, are transported in large quantities to the liver via the portal vein, where they are accumulated as ectopic fat, thus leading to the development of non-alcoholic steatohepatitis (NASH). There
is a unique histological feature termed “hepatic CLS (hCLS)” in the NASH liver, where macrophages aggregate to surround dead hepatocytes with large lipid droplets. Notably, the number of hCLS is positively correlated with the extent of liver fibrosis. Our data suggest that hCLS serves as an origin of hepatic inflammation and fibrosis during the progression from simple steatosis to NASH.

We postulate that CLS/hCLS represent the unique microenvironment for parenchymal-stromal cell interaction in metabolic diseases, thus providing a promising target of new drug discovery and development.