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Chronic pancreatitis: an inflammatory disease of pancreas

Pancreas is very important organ in our body and it is located in the abdomen behind the stomach. Pancreas is a gland and secrets some chemicals called enzymes. It is a leaf like structure and divided in two parts such as endocrine and exocrine. The endocrine part secretes of insulin and glucagon enzymes that maintains our body's glucose metabolism. The exocrine part of pancreas secretes several digestive enzymes such as amylase, lipase, pepsin needed for digestion of food that we have routinely.

Pancreatitis is an inflammation of pancreas arises due to several reasons such as blockade of pancreatic duct, drinking alcohol, certain drugs, and some time hereditary. Pancreatitis can be further subdivided in to acute pancreatitis (AP) and chronic pancreatitis (CP). AP is an early onset of disease with symptoms of stomach pain, fever, nausea, vomiting; whereas, chronic pancreatitis develop due to repeated episodes of acute pancreatitis and characterized by the development of pancreatic fibrosis. The incidence of acute and chronic pancreatitis is increasing day by day and it is also a major cause to increase the burden of hospitalization in the case of acute pancreatitis and mortality due to chronic pancreatitis. The annual incidence of acute pancreatitis varies from 13 to 45 per 100000 people in United States, whereas chronic pancreatitis ranges from 4.4 to 11.9 per 100000 per year. However, the global annual cases of pancreatic cancer are about 8 per 100,000 people.

The pathogenesis of chronic pancreatitis involves variety of immune cells and some proteins called cytokines or interleukins. During pancreatic inflammation several inflammatory cytokines such as interleukin (IL)-1, IL-6, IL-8, IL-18, IL-33, and tumor necrosis factor-α are secreted from immune cells. These immune cells are mainly monocytes, macrophages, dendritic cells, natural killer cells, T cells, mast cells etc. Apart from these cells, some non-immune cells such injured acinar cells and pancreatic stellate cells (PSCs) play very critical role in disease pathogenesis and leads pancreatic fibrosis. Pancreatic fibrosis is the deposition of collagen fibers that makes fibrous connective tissue during chronic inflammation of the pancreas that leads calcification and hardening of the tissue. Pancreatic fibrosis is a major concern for the successful treatment of chronic pancreatitis and pancreatic cancer. Therefore, restriction in the progression of fibrosis is the promising approach to manage the pancreatitis pathogenesis.

Role of eosinophils in chronic pancreatitis

Recently, we have shown the important role of eosinophils i.e a type of subset of immune cell that have an important role in promoting fibrosis. They are generated in the bone marrow and have important role in our immune system. The healthy pancreas is devoid of eosinophils and our findings provided the evidence that increased eosinophil accumulation takes place in the pancreas of cerulein-induced chronic pancreatitis mouse model (Cerulein is chemical known to induce pancreatitis in mouse). The induction of eosinophil specific cytokines i.e. IL-5, IL-18, and eosinophil specific chemokines i.e Eotaxin 1 and Eotaxin 2 were found during chronic pancreatitis. These observations suggest that the increased expression of these cytokines and chemokines attracts eosinophils in chronically inflamed pancreas. The accumulated eosinophils also lead induction of pro-fibrotic gene called Transforming Growth Factor Beta 1 (TGFβ1) and PSCs specific marker called alfa-smooth muscle actin (α -SMA). Our finding further suggests that eosinophils have critical role in the progression of pancreatic fibrosis during chronic inflammation of pancreas. It is interesting to note that eosinophils deficient mice show less fibrosis after cerulein-induced chronic pancreatitis.

Protective effect of IL-15 in chronic pancreatitis

Furthermore, in another study we reported the protective role of interleukin (IL)-15 in a mouse model of chronic pancreatitis. IL-15 is a cytokine implicated in innate and acquired antiviral immunity. IL-15 receptors are expressed on dendritic cells, monocytes, natural killer (NK) cells. Our study show that IL-15-mediated increase of interferon-gamma-responsive invariant natural killer T (iNKT) cells protects cerulein-induced pancreatic pathogenesis in mice. IL-15 treatment also reduces fibrosis associated genes such as TGFβ1, α-SMA, collagen and fibronectin in these experimental mice suggesting that IL-15 has anti-fibrotic potential and IL-15 agonist may be a novel therapeutic strategy for chronic pancreatitis and associated fibrosis.

Immune cells (eosinophils) and cytokines (IL-15) are the important key players during the pathogenesis of chronic pancreatitis and future therapy.

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Publications

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