Iron drives T helper cells pathogenicity by promoting RNA-binding protein PCBP1-mediated proinflammatory cytokine production

With the support by the National Natural Science Foundation of China, a research team directed by Prof. Chang Xing (常兴) at the Shanghai Institute of Nutrition and Health, Chinese Academy of Sciences, recently reported that intracellular iron drives autoimmune disease by increasing proinflammatory cytokine production in T cells. Moreover, they demonstrated that an RNA-binding protein PCBP1 bridges iron metabolism and cytokine expression in T cells through post-transcriptional mechanisms. This study was published in *Immunity* (2018, 49: 1—13).

Autoimmune diseases are disorders that the immune system mistakenly attacks and damages self-tissues. There are more than 100 autoimmune diseases, affecting approximately 5%—8% of the population in the world. Unfortunately, there are few effective treatments to autoimmune diseases, mainly due to the poor understanding of these diseases. A long but little understood clinical observation is that excessive iron is frequently found in human autoinflammatory diseases, such as in the central nervous system of patients with multiple sclerosis. Yet, the functional outcome of excessive iron in the auto-inflammatory response is largely unknown.

The researchers led by Dr. Chang demonstrated that iron was able to directly participate in inflammatory responses by promoting proinflammatory cytokine production in the T(h) cells via poly(rC)-binding protein 1 (Pcbp1), an RBP with iron chaperon activity. They showed that intracellular iron depletion or Pcbp1 deficiency in autoreactive T cells resulted in shortened mRNA half-life and diminished GM-CSF production, protecting mice against EAE, a murine model of human autoimmune disease, multiple sclerosis. Conversely, iron overload induced by iron dextran enhanced GM-CSF production of T cells via Pcbp1. Mechanistically, intracellular iron protected Pcbp1 protein from caspase-mediated proteolysis, and Pcbp1 promoted mRNA stability by recognizing UC-rich elements in the 3'UTRs. Thus, these results suggest a model that excessive iron may directly precipitate autoimmune diseases through post-transcriptional regulation of pro-inflammatory cytokine expression in T cells.

These findings may provide considerable new insights into the molecular pathogenesis of autoimmune disorders and may provide new therapeutic targets in autoimmune disease prevention and treatment.

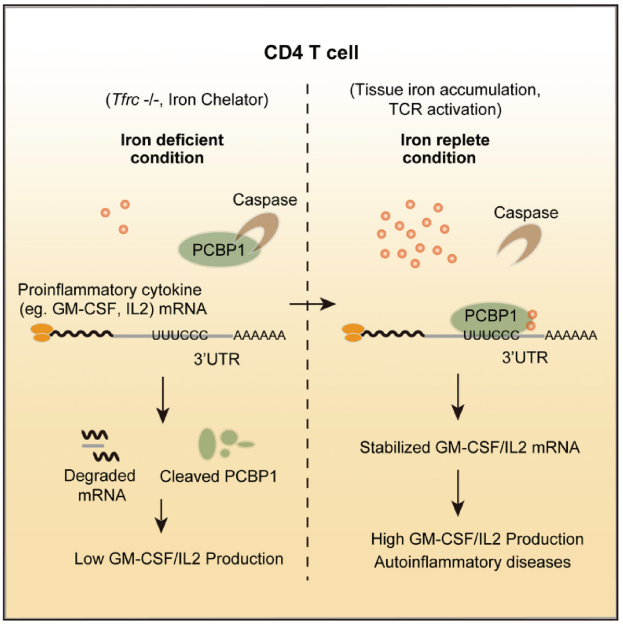

Figure In the absence iron, PCBP1 protein was degraded, resulting in reduced mRNA stability and diminished production of GM-CSF (left). In contrast, when excessive iron accumulates, increased intracellular iron stabilizes PCBP1 and drives GM-CSF production in autoinflammatory diseases (i.e. Multiple Sclerosis).