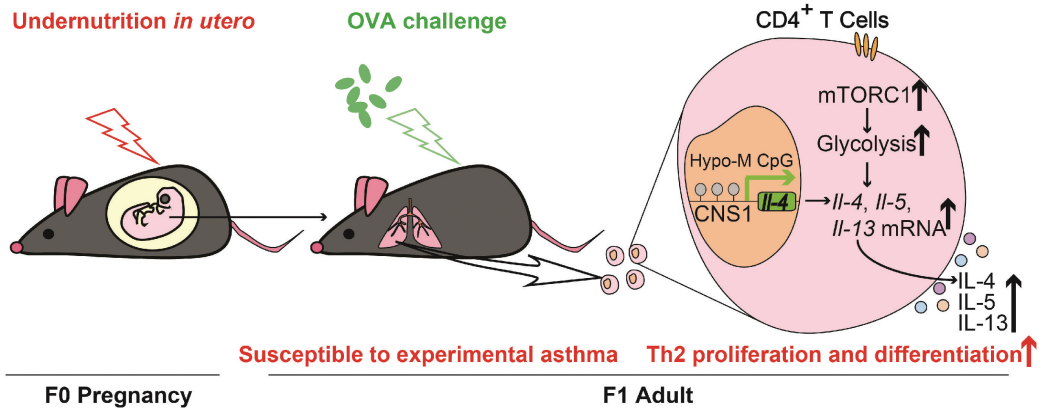
Early life undernutrition reprograms CD4$^+$ T-cell glycolysis and epigenetics to facilitate asthma

With the support by the National Natural Science Foundation of China, the research team directed by Prof. Huang HeFeng (黄荷凤) at Shanghai Key Laboratory of Embryo Original Disease, Institute of Embryo Fetal Original Adult Disease and International Peace Maternity & Child Health Hospital, School of Medicine, Shanghai Jiao Tong University, recently reported the capacity of maternal diets to remodel cell-intrinsic metabolic pathways and epigenetics within offspring immune cells, which was published in *Journal of Allergy and Clinical Immunology* (doi: 10.1016/j.jaci.2018.12.999. Epub ahead of print).

Early life undernutrition is associated with an increased risk of asthma throughout childhood and into adulthood. However, the underlying mechanisms of this susceptibility to asthma are poorly characterized. Asthma involves chronic allergic airway inflammation, where type 2 T helper (Th2) cells play a fundamental role. Although animal models and clinical studies have suggested maternal diets can influence offspring CD4$^+$ T-cell functions, the role of maternal malnutrition in T-cell functions and differentiation remains unclear.

To explore whether early life undernutrition altered T-cell functions, they employed a maternal protein restriction mice model. And they analyzed CD4$^+$ T-cell functions and asthma phenotypes of offspring from breeders fed a normal chow diet (NCD) or protein restriction diet (PRD). They found that, in the early life undernutrition model, CD4$^+$ T cells displayed enhanced activation and proliferation and were prone to differentiate toward Th2 cells both *in vitro* and *in vivo*, resulting in susceptibility to OVA-induced experimental asthma. Mechanistically, early life undernutrition accelerates mTORC1-dependent glycolytic activity in T cells, resulting in Th2 skewing and susceptibility to OVA-induced experimental asthma. Glycolysis blockades undermined increased Th2 skewing and alleviated experimental asthma in PRD mice. Moreover, naïve CD4$^+$ T cells exhibit pre-existing signs of DNA demethylation in the CNS1 region of Th2 cytokine locus and are inclined to secrete more Th2 cytokines when exposed to maternal malnutrition.

Their study provides direct evidence showing that early life undernutrition leads to perturbed CD4$^+$ T-cell differentiation and functioning in a cell-intrinsic manner, resulting in susceptibility to experimental asthma, and offering new insights into the pathogenesis of other developmental origins of adult disease.



CNS1	Conserved noncoding DNA sequence 1	**Hypo-M CpG**	Hypomethylated CpG
mTORC1	The mechanistic target of rapamycin 1	**OVA**	Ovalbumin

Figure Working model for the mechanisms of early life undernutrition reprograms CD4$^+$ T-cell functions to facilitate asthma.