Molecular basis of fever boosting immune cell trafficking

With the support by the National Natural Science Foundation of China, the National Basic Research Program of China, the Chinese Academy of Sciences, and the China Postdoctoral Science Foundation, the research team led by Prof. Chen JianFeng (陈剑峰) at Shanghai Institute of Biochemistry and Cell Biology of Chinese Academy of Sciences, uncovers a mechanism to explain how fever promotes T lymphocyte trafficking and enhances immune surveillance during infection through a thermal sensory heat shock protein 90 (Hsp90)-α4 integrin pathway, which was published in *Immunity* (2019, 50: 137—151).

Fever is a highly conserved response to infection or injury and benefits organism survival and the resolution of many infections. Emerging evidence suggests that fever-range thermal stress (38—40℃) plays an active role in directing migration of immune cells into secondary lymphoid organs or inflammatory sites. However, whether and how fever can regulate the function of integrins, the key cell adhesion molecules in mediating immune cell trafficking, has remained obscure.

By using T cells from mice, Chen's group found that fever (38.5℃ and above) increased Hsp90 expression in T cells and promoted α4 integrin-mediated T cell adhesion and transmigration. Further studies revealed that Hsp90 bound to α4 tail and activated α4 integrins via inside-out signaling. Moreover, the N and C termini of one Hsp90 molecule simultaneously bound to two α4 tails, leading to dimerization and clustering of α4 integrins on cell membrane and subsequent activation of FAK-RhoA pathway to promote T cell migration. They then generated a knock-in mice line to disrupt Hsp90-α4 interaction *in vivo* and used several fever mouse models to study the biological function of Hsp90-α4 integrin pathway. They found abolishment of Hsp90-α4 interaction significantly inhibited fever-induced T cell trafficking to draining lymph nodes and impaired the clearance of *Salmonella typhimurium* infection. In addition to T cells, this mechanism also can apply to different immune cells expressing α4 integrins like monocytes, B cells, etc., suggesting its general roles in both innate and adaptive immune response. These findings identify Hsp90-α4 integrin axis as a novel thermal sensory pathway that promotes immune cell trafficking and enhances immune surveillance during infection. The molecular basis revealed in the *Immunity* paper could lead to the development of strategies for the management of diseases by enhancing or tempering immune cell trafficking.

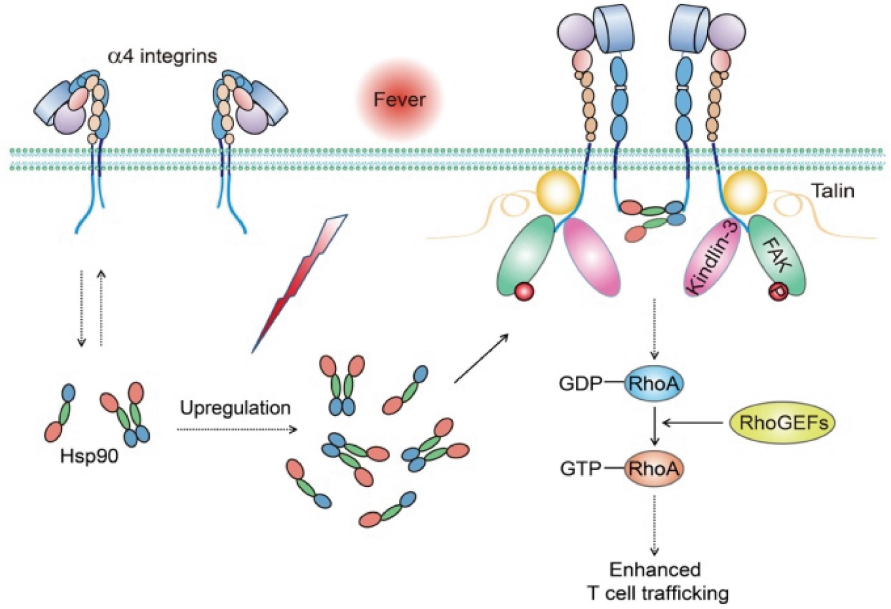

Figure Schematic diagram of fever promoting T cell trafficking.