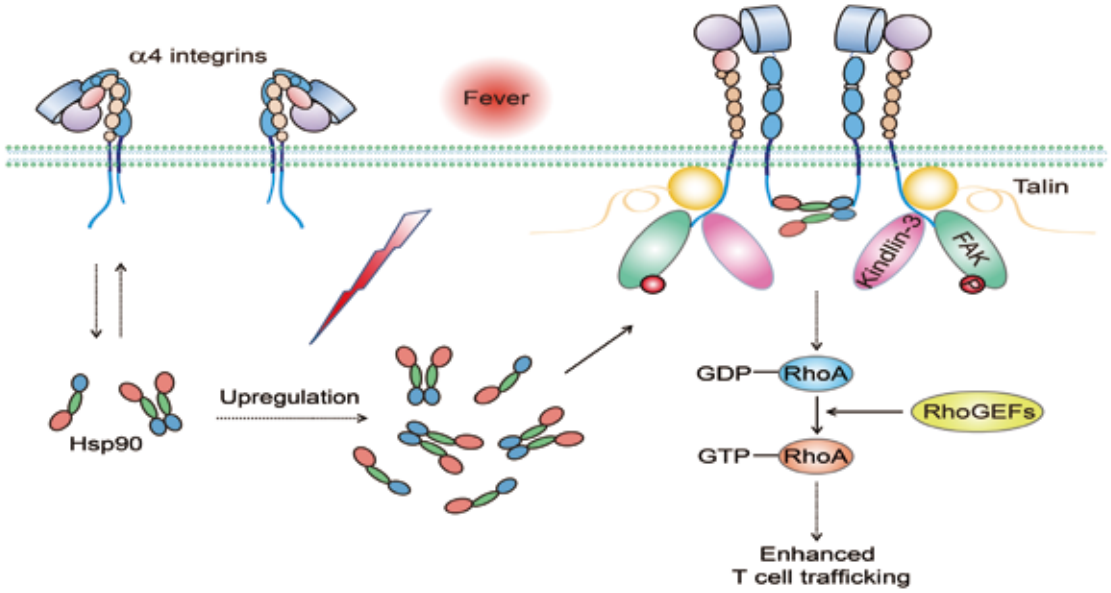
Look on the Bright Side of Fever

By YAN Fusheng (Staff Reporter)

Fever is a state of elevated body temperature, one of the most common signs of infections caused by viruses, bacteria or parasites. Despite the heat and dizziness it causes, fever is actually in alliance with the body's immune system to fight these pathogens. CAS researchers reported online 15th January in *Immunity*, that fever in mice can alter membrane proteins on immune cells like T cells to enhance their ability to enter infection sites or lymph nodes. These immune cells can either directly march into the battle field of the infection or learn to recognize the enemies in the lymph node before joining the battle. In either case, a stronger army of immune cells will gather at the infection site, and lead to a quicker clearance of the pathogens.

All mammals can develop fever when they're sick from infections, and even cold-blooded animals, such as lizards and a small number of fish, will seek warmth to raise their body temperatures when they're infected. This suggests that fever is a shared defensive response that somehow helps the body fight infection-causing pathogens. Recently, a new molecular picture of how immune cells sense fever and use it to enhance their own strength was illustrated by a CAS research team led by Prof. CHEN Jianfeng at the **CAS Shanghai Institute of Biochemistry and Cell Biology (SIBCB)**.

To get rid of an infection, circulating immune cells need to adhere to and transmigrate across the walls of the vessels, known as high endothelial venules (HEVs) to enter



How does fever do a good deed for T cells? Fever upregulates the expression of heat shock protein 90 (Hsp90), one type of molecular chaperones that assist other proteins to fold into a functional conformation. These proteins then dock onto the cytoplasmic tails of α4 integrins, a type of adhesion molecules, which then enhances T cell adhesion and transmigration into infected tissues or lymph nodes. As a result, more immune cells can be mobilized to the infection site to kill pathogens. (Credit: Prof. CHEN Jianfeng, SIBCB)

an infection site or lymph node. Adhesion molecules on immune cells and ligands on HEV cells are necessary for the immune cells to accomplish these movements.

Early studies have shown that fever can increase the levels of an adhesion molecule ligand named intercellular adhesion molecule 1 (ICAM-1), and chemokine (C-C motif ligand 21, CCL21) on HEV cells. Because of this, T cells can stick more tightly to HEV cells. As a result, more T cells can enter into lymph nodes. However, little is known about what kind of changes fever can make on T cells, which in the end reinforces the body's immune system against infection-causing pathogens.

Scientists turned their attention to integrins, one type of adhesion molecules expressed on the plasma membrane of T cells, given that integrins directly mediate the adhesion of T cells onto HEV cells. Previous efforts have revealed that integrins are transmembrane heterodimers, consisting of α and β subunits, where each subunit has a cytoplasmic tail for the docking of other proteins from inside, and extracellular "hand-like" domain mediating the contact with other cells.

In an effort to reveal what fever can do on these integrins and its relevance to convey the bright side of fever, the team identified a novel thermal sensory pathway in T cells, the "Hsp90-α4-integrin axis." In this pathway, T cells sense the fever and upregulate heat shock protein 90 (Hsp90), one type of molecular chaperones that assist other proteins to fold properly and function normally under stressful conditions, such as fever in this case. These Hsp90 proteins were found to bind to the cytoplasmic tail of α4 integrins from the inside. Upon the binding of Hsp90, the extracellular parts of integrins make a structural (functional as well) change from the bent state (inactive) into the extended state (active). Upon activation, integrins stretch themselves to get ready to dock onto other ligands on HEV cells. By means of this inside-out signaling of the Hsp90-α4-integrin pathway, fever enables T cells to stick more tightly onto the vessels at the infection site or lymph node.

The team also found that one molecule of Hsp90 can actually bind to two cytoplasmic tails of α4 integrins, and thus trigger the dimerization and clustering of these integrins. The clustering integrins then activate some downstream pathway inside that revs up the cytoskeleton dynamics and spurs the cell into spreading and crawling. In other words, fever makes T cells better able to cross the vessels. As a result, more immune cells can gather within an infection site or lymph node.

In the end, the team examined whether the Hsp90-α4-integrin pathway is indispensable for conveying these fever-induced benefits in mouse models. In this regard, they generated genetically modified (GM) mice to specifically disrupt the binding between Hsp90 and α4 integrins, while the expression of integrins was found to remain unchanged. As compared to the wide-type mice, the fever-enhanced T cell distribution at lymph nodes was abolished in the GM mice. Consistently, using mice fever models, the researchers found that, unlike the wide-type mice, the GM mice failed to achieve effective clearance of bacterial infection and died quickly. Hence, the researchers concluded that the Hsp90-α4-integrin pathway is indispensable for conferring the benefits of fever or febrile stress.

Notably, the researchers also found that the Hsp90-α4-integrin pathway is very temperature-dependent. Moderate fever (~38°C) caused by injecting lipopolysaccharide, a kind of endotoxins associated with the outer membrane of Gram-negative bacteria, does not change Hsp90 expression or T cell distribution in mice. Temperatures above 38.5°C were, however, shown to enhance Hsp90 expression, as demonstrated by an in vitro study. So, it appears that high fever above 38.5°C is required to deliver the benefits of fever.

No sweet without sweat

In short, the researchers discovered that fever can alter membrane proteins on T cells, mobilize them into the infection site or lymph node, and hence facilitate clearance of pathogens. The activation of a thermal sensory pathway, the Hsp90-α4-integrin axis, was found to be crucial in conferring fever-induced benefits. This thermal sensory pathway and its resultant benefits upon fever could be shared by other immune cells carrying α4 integrins on their plasma membrane, suggested the researchers. An intensified gathering of various immune cells at the infection site can power up the immune strength against pathogens. Hence, a necessary suffering from fever could repay the body well.

"The abnormality of immune cell infiltration may cause chronic inflammation and autoimmune disorders," suggested the researchers, "however, this Hsp90-α4-integrin pathway offers a leverage for medical managements. In this case, inhibiting the pathway can reduce the abnormal immunity and therefore alleviate the symptoms of these disorders. On other occasions, upregulating Hsp90 expression in immune cells may power up immune response to fight infection or even cancers."

Reference

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