MST4 Revealed a Molecular Brake to Prevent Overactive Inflammatory Responses

Innate immunity is the frontline of defense against pathogens. Upon detection of pathogen-associated molecular patterns, Toll-like receptors (TLRs) will initiate innate immune responses, like inflammation, via activating the adaptor molecule TRAF6 to remove pathogens. However, excessive or prolonged inflammatory responses can cause severe host damage or even death; meanwhile chronic inflammation could lead to the development of tumors. Thus the balance between inflammation and tolerance must be fine maintained.

TLR-TRAF6 signaling has been extensively investigated due to its critical roles in inflammation and cancer. Yet increasing studies suggest a picture of TLR-TRAF6 pathways far more complicated than previously thought. Now, a research group led by Prof. ZHOU Zhaocai from the Institute of Biochemistry and Cell Biology, Shanghai Institutes for Biological Sciences, CAS identified the kinase MST4 as a "brake" molecule that dynamically responds to inflammatory stimuli. Analyzing clinical samples of sepsis and malaria, researchers found that MST4 expression was dysregulated in these infectious diseases. MST4 expression displayed a dramatic fluctuation upon inflammatory stimulation, and such kinetics is correlated with inhibition of inflammatory cytokine production. Mechanistically, MST4 directly interacts with and phosphorylates TRAF6 to restrict its auto-ubiquitination and signaling activity. Thus, the researchers suggested, MST4 could act as a "brake" on TLR-TRAF6-mediated inflammatory responses. Analyses in mouse model of sepsis confirmed these findings, and further revealed that MST4 might protect the host from septic shock largely through macrophage. This study proposed a new mechanism in controlling innate immunity, and may also provide some new clues for the pathogenesis of some inflammation-related diseases, including cancer.

This work, entitled "*The kinase MST4 limits inflammatory responses through direct phosphorylation of the adaptor molecule TRAF6*", was published online in *Nature Immunology* on Feb 2nd, 2015.

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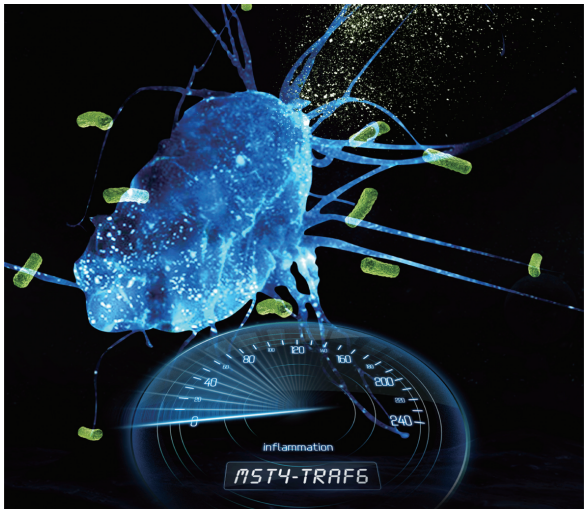
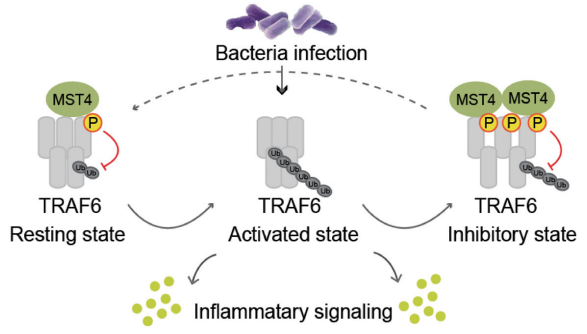


Inflammation, a mechanism of immune system, helps the body to get rid of harmful damages, including pathogens. Excessive or prolonged inflammatory responses, however, could lead to septic shock or even death. How organisms maintain a sophisticated balance between inflammation and tolerance has baffled scientists. A team led by Prof. ZHOU Zhaocai at the Shanghai Institute of Biochemistry and Cell Biology, Shanghai Institutes for Biological Sciences, CAS lately unveiled a molecular brake in the innate immunity to prevent over reactions: the germinal center kinase MST4.



MST4 limits inflammatory response via inhibition of TLR-TRAF6 signaling. (Image by courtesy of Prof. ZHOU Zhaocai)

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