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Brief Introduction:

Dr. Feng Shao is an investigator and deputy director at National Institute of Biological Sciences (NIBS), Beijing, China. He was a chemistry undergraduate of Peking University (1991-1996) and obtained his PhD with Dr. Jack E. Dixon from University of Michigan in 2003. Prior to returning to China in 2005 to assume an assistant investigator at NIBS, he was a Damon Runyon Postdoc Research Fellow at Harvard Medical School. Dr. Shao was promoted to become an associate investigator in 2009 and a full investigator in 2012 at NIBS. He has also been appointed as an Endowed Chair Professor of Tsinghua University since 2020.

Dr. Shao's research lies at the interface between bacterial pathogen and host inflammation. He identified most of the known cytosolic receptors for bacterial molecules, including caspase-11/4/5 for LPS and ALPK1 for ADP-heptose in LPS biosynthesis. He also identified gasdermin-D (GSDMD) whose cleavage by caspase-1/4/5/11 determines pyroptosis, critical for septic shock and other inflammatory diseases. His research establishes the gasdermin family of pore-forming proteins, re-defining pyroptosis as gasdermin-mediated programmed necrosis. Among the family, GSDME is activated by caspase-3, which occurs mostly in noncancer cells and contributes to toxicity of chemotherapy drugs. His most recent work demonstrates that pyroptosis is a critical mechanism underlying lymphocyte cytotoxicity and gasdermin activation can stimulate potent antitumor immunity.

Title: Activation of antitumor immunity by bacteria-derived signals: Pyroptosis & Beyond

Abstract:

Pyroptosis is a proinflammatory cell death executed by the gasdermin-family pore-forming proteins. Among the family, gasdermin D (GSDMD) is cleaved by inflammasome-activated caspase-1 and LPS-activated caspase-11/4/5. The cleavage unmasks the pore-forming domain in GSDMD that perforates plasma membrane. Using a bioorthogonal chemical biology approach allowing controlled delivery of active gasdermin into tumors in mice, we found that pyroptosis of < 15% tumour cells could clear the entire 4T1 mammary tumor graft, which was absent in immune-deficient mice or upon T-cell depletion. Thus, pyroptosis stimulates potent and effective antitumour immunity. In antitumor immunity, cytotoxic lymphocyte relies on granzymes to kill target cells. We found that natural killer cells and cytotoxic T lymphocytes kill GSDMB-positive cells through pyroptosis, mediated by granzyme A (GZMA) cleavage of GSDMB. IFN-γ upregulates GSDMB expression and promotes pyroptosis of cancer cells including that by CAR-T/TCR-T cells. Thus, gasdermin-executed pyroptosis serves as a cytotoxic lymphocyte killing mechanism, playing an important role in cancer immunotherapy. We recently discovered a novel cytosolic innate immune receptor alpha-kinase 1 (ALPK1) that

recognizes a bacterial metabolite ADP-heptose. ADP-heptose-activated ALPK1 phosphorylates the TIFA adaptor, thereby stimulating the NF-κB signaling and proinflammatory cytokine production. I will also discuss the function of ALPK1-TIFA axis in cancer immunity.

Representative publications (#corresponding authors):

1. Zhong X, Zeng H, Zhou Z, Su Y, Cheng H, Hou Y, She Y, Feng N, Wang J, Shao F#, and Ding J# (2023) Structural mechanisms for regulation of GSDMB pore-forming activity. *Nature*, 616, 598-605.
2. Li Z, Liu W, Fu J, Cheng S, Xu Y, Wang Z, Liu X, Shi X, Liu Y, Qi X, Liu X#, Ding J, Shao F# (2021) Shigella evades intracellular LPS-induced pyroptosis by arginine ADP-riboxanation of caspase-11. *Nature*, 599, 290-295.
3. Zhou Z, He H, Wang K, Shi X, Wang Y, Su Y, Wang Y, Li D, Liu W, Zhang Y, Shen L, Han W, Shen L, Ding J, Shao F# (2020). Granzyme A from cytotoxic lymphocytes cleaves GSDMB to trigger pyroptosis in target cells. *Science*, 368(6494):eaaz7548.
4. Wang Q, Wang Y, Ding J, Wang C, Zhou X, Gao W, Huang H, Shao F# & Liu Z# (2020) A bioorthogonal system reveals antitumour immune function of pyroptosis, *Nature*, 579, 421-426.
5. Wang K, Sun Q, Zhong X, Zeng M, Zeng H, Shi X, Li Z, Wang Y, Zhao Q, Shao F# and Ding J# (2020) Structural Mechanism for GSDMD Targeting by Autoprocessed Caspases in Pyroptosis, *Cell*, 180, 941-955.

More info on Dr. Feng Shao's work:
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