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The Second Generation of Tyrosine Kinase Inhibitor Afatinib Controls Inflammation by Regulating NLRP3 Inflammasome Activation

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Abstract : Background: Chronic inflammation might lead to many malignancies, and inadequate resolution could play a crucial role in tumor invasion, progression, and metastases. A randomised, double-blind, placebo-controlled trial shows that IL-1β inhibition with canakinumab could reduce incident lung cancer and lung cancer mortality in patients with atherosclerosis. The process and secretion of proinflammatory cytokine IL-1β are controlled by the inflammasome. Here we showed the correlation of the innate immune system and afatinib, a tyrosine kinase inhibitor targeting epidermal growth factor receptor (EGFR) in non-small cell lung cancer. Methods: Murine Bone marrow derived macrophages (BMDMs), peritoneal macrophages (PMs) and THP-1 were used to check the effect of afatinib on the activation of NLRP3 inflammasome. The assembly of NLRP3 inflammasome was check by co-immunoprecipitation of NLRP3 and apoptosis-associated speck-like protein containing CARD (ASC), disuccinimidyl suberate (DSS)-cross link of ASC. Lipopolysaccharide (LPS)-induced sepsis and Alum-induced peritonitis were conducted to confirm that afatinib could inhibit the activation of NLRP3 in vivo. Peripheral blood mononuclear cells (PBMCs) from non-small cell lung cancer (NSCLC) patients before or after taking afatinib were used to check that afatinib inhibits inflammation in NSCLC therapy. Results: Our data showed that afatinib could inhibit the secretion of IL-1β in a dose-dependent manner in macrophage. Moreover, afatinib could inhibit the maturation of IL-1β and caspase-1 without affecting the precursors of IL-1β and caspase-1. Next, we found that afatinib could block the assembly of NLRP3 inflammasome and the ASC speck by blocking the interaction of the sensor protein NLRP3 and the adaptor protein ASC. We also found that afatinib was able to alleviate the LPS-induced sepsis in vivo. Conclusion: Our study found that afatinib could inhibit the activation of NLRP3 inflammasome in macrophage, providing new evidence that afatinib could target the innate immune system to control chronic inflammation. These investigations will provide significant experimental evidence in afatinib as therapeutic drug for non-small cell lung cancer or other tumors and NLRP3-related diseases and will explore new targets for afatinib.

Keywords : inflammasome, afatinib, inflammation, tyrosine kinase inhibitor
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