**Wiskott-Aldrich Syndrome Protein Regulates Autophagy and Inflammasome Activity in Innate Immune Cells**

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Abstract

Dysregulation of autophagy and inflammasome activity contributes to the development of auto-inflammatory diseases. Emerging evidence highlights the importance of actin cytoskeleton in modulating inflammatory responses. Wiskott-Aldrich syndrome (WAS) is an X-linked recessive primary immunodeficiency disorder characterized by microthrombocytopenia, defective immunity and eczema. Autoimmune disorders occur in 20-70% of patients with WAS; common manifestations include autoimmune haemolytic anaemia, neutropenia, vasculitis, arthritis and inflammatory bowel disease. There are some features of WAS that resemble paradigmatic auto-inflammatory syndromes, but this has not been mechanistically explored. We tested the hypothesis that deficiency of the WAS protein (WASp) which signals to the actin cytoskeleton through the actin nucleating complex Arp2/3, modulates autophagy and inflammasome function. In a model of sterile inflammation utilizing Toll-like receptor 4 ligation followed by treatment with ATP or nigericin, we observed enhanced inflammasome activation in monocytes from WAS patients and in WAS knockout murine bone marrow-derived dendritic cells. In *ex-vivo* models of enteropathogenic *Escherichia coli* or *Shigella flexneri* infection, WASp deficiency resulted in defective bacterial clearance, exaggerated inflammasome activation and increased host cell death. These events were associated with dysregulated septin cage-like formation and impaired autophagic p62/LC3 recruitment and defective formation of canonical autophagosomes. Taken together, we propose that dysregulation of the autophagy and inflammasome activities partly contribute to the autoinflammatory manifestations of WAS, thereby offering targets for potential therapeutic intervention.