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COMMENTARY

An Old Molecule with a New Role: Microtubules in Inflammasome Regulation

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A commentary on "Microtubule-driven spatial arrangement of mitochondria promotes activation of the NLRP3 inflammasome" by Misawa et al. (2013) Nature Immunology Volume: 14, Pages: 454–460 Year published

Microtubules are a major component of cytoskeletal systems that are involved in the regulation and distribution of mitochondria in mammalian cells [1]. These tubular polymers regulate the distribution of several cell organelles such as endoplasmic reticulum, Golgi, peroxisomes, and lysosomes. However, aberrant expression of these microtubules can alter the mitochondrial distribution and dysfunction of these organelles and result in diseases like Alzheimer's, Parkinson's, and cancer [2]. A study by Mirzapoiazova et al. [3] also demonstrated that microtubule stabilization with taxol systemically attenuates lipopolysaccharide-induced inflammation and vascular leak. Furthermore, studies present microtubules to be directly involved in neutrophil locomotion, leukocyte transmigration, and solute permeability in several inflammation-related lung disorders such as Acute Lung Injury (ALI). In recent years, there has been growing evidence that inflammasomes mainly act as danger-sensing signals and orchestrate inflammatory signaling in several inflammation-related disorders [4–8]. Inflammasomes are multiprotein, high molecular weight complexes that are localized in the cytosol of cells and display an enzymatic activity that activates the cytokine IL-1beta (IL-1β) [9]. There are several theories on the mechanism of inflammasome activation, but there is limited information on the mechanism in which microtubules alter the inflammatory regulators.

A recent study by Misawa et al. [10] observed an interesting link between microtubules and inflammasomes. In their study, the authors demonstrated that inhibitors of microtubule polymerization like colchicine and nocodazole can lead to the decrease in production of IL-1β, a major pro-inflammatory cytokine processed and secreted by the NLRP3 inflammasome. Interestingly, the activation of the NLRP3 inflammasome was not dependent of the phagocytic pathway but was due to the microtubule-mediated relocalization of mitochondria. Mitochondria are transported via motor proteins like kinesin and dynein along the microtubules. To further analyze the role of microtubule-associated inflammasome activation, Misawa et al. assessed the interactions of dynein—a motor protein that interacts with microtubules through acetylated α-tubulin. ASC is an adaptor protein (present on the mitochondria), required for the inflammasome assembly, that failed to get recruited to NLRP3 when α-tubulin acetylation was inhibited. To further investigate the role of acetylated α-tubulin in the activation of NLRP3 inflammasome, Misawa et al. knocked down an acetyltransferase called MEC-17 which, in turn, suppressed the localization of ASC to NLRP3 and subsequent production of IL-1β in response to NLRP3 inflammasome activators. The authors presented intriguing data that implicate the co-factor NAD^+ in promoting the NLRP3 inflammasome activation. Narayan et al., in their previous reports, presented the role of SIRT2 which is an enzyme involved in mediating the complex

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formation. The activity of SIRT2 is dependent on its co-factor NAD^+ [11]. The lower levels of NAD^+ indicated higher acetylation of α-tubulin which further leads to increased perinuclear localization of mitochondria in cells. Yet, little is understood about the role of microtubules in mitochondria-mediated inflammasome activation. A previous report by Zhou et al. [12] has shown that during the activation of the NLRP3 inflammasome complex, ASC on the mitochondria localizes together with exogenously transduced NLRP3 on the endoplasmic reticulum in monocytes. Zhou et al. demonstrated that NLRP3 activators caused a reduction in NAD^+ levels by decreased mitochondrial membrane potential and damage to the mitochondria. Their findings provided key mechanistic insight of how microtubules mediated the transport of mitochondria to create optimal sites for the activation of NLRP3 inflammasome. Mechanisms that regulate inflammasome activation still remain elusive. Misawa et al. reveal a new role in the regulation and association of the NLRP3 complex formation via microtubule–mitochondrial interactions. They identified a novel mechanism of microtubule-dependent assembly of the NLRP3 inflammasome. The relevance of findings by Misawa et al. is fascinating; however, it is likely that there might be other structural proteins that can connect the mitochondrial ASC and NLRP3 together; although Misawa et al. ruled out the possibility of microtubules in the activation of the NLRC4 and AIM2 inflammasomes [10, 13].

The regulation of IL-1β processing and secretion is still unknown but revealing the mechanism to these can provide new therapeutic targets to NLRP3-mediated inflammatory disorders. Microtubule-mediated inflammasome organization and activation is currently being explored to seek out cues to tackle inflammation-mediated diseases in humans. A combinatorial approach of using microtubule and inflammasome inhibitors may provide a broader spectrum of potential targets and therapy for inflammasome-related disorders in addition to the IL-1β inhibition which is currently being implemented. As research continues, it is also probable that other cytoskeletal molecules might be involved in the assembly and activation of these complexes. The authors suggest a calorie-restricted diet with removal of damaged mitochondria or elimination of mediators that localize the microtubule-mediated inflammasome complex formation. This could be an effective treatment for NLRP3-related inflammatory disorders.

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