**Pleiotropic signaling actions of inositol polyphosphate metabolism**

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**Abstract**

Hydrolysis of phosphatidylinositol 4,5-bisphosphate by phospholipase C produces diacylglycerol and inositol 1,4,5-trisphosphate (IP3). Biological actions of inositol phosphate kinases and their inositol polyphosphate (IP) products are highlighted to mediate a diverse range of cellular events such as growth. Among many IPs in mammalian cells, inositol pyrophosphates such as 5-IP7 (5-diphosphoinositol pentakisphosphate) are highly energetic IP harboring phosphoanhydride bonds. I will discuss our recent work demonstrating that 5-IP7 acts through Synaptotagmin-1 (Syt1) binding to interfere with the fusogenic activity of calcium in the control of vesicle membrane fusion. The data reveal a role of 5-IP7 as a potent inhibitor of Syt1 in regulating the synaptic exocytotic pathway. Analyses of inositol hexakisphosphate kinase 1 (Ip6k1)-knockout hippocampal neuron further showed increased presynaptic release probability, implying 5-IP7-mediated control of synaptic vesicle exocytosis. Other lines of recent evidence will be also presented and discussed to propose that one of inositol polyphosphate biosynthetic enzymes called IPMK (Inositol polyphosphate multikinase) is intimately linked to the fine control of immune responses. We demonstrate that myeloid-specific deletion of inositol polyphosphate multikinase (IPMK), which possesses both inositol polyphosphate kinase activities and non-catalytic signaling functions, protects mice against polymicrobial sepsis as well as lipopolysaccharide (LPS)-induced systemic inflammation. Mechanistically, the regulatory role of IPMK is independent of its catalytic function, instead reflecting its direct binding to TRAF6. On the other hand, IPMK deletion in B cells can catalytically mediate their LPS-induced proliferation as well as function via IPMK-mediated IP6 production. IPMK-controlled IP6 turns out a key signaling metabolite in the activation of Btk. We further expect that therapeutics that modulate the levels of IP6K/IPMK or its signaling activities will be useful in the management of uncontrolled inflammation or neuromodulation. Future directions of IP metabolism in health and disease will be reviewed and highlighted during this presentation.

**Keywords**:

Inositol polyphosphate, IP7, synaptic vesicle cycling, IPMK, IP6, inflammation, Btk