Nuclear Delivery of Inositol Pyrophosphate Prometabolites Mediated by Short Cationic Peptides

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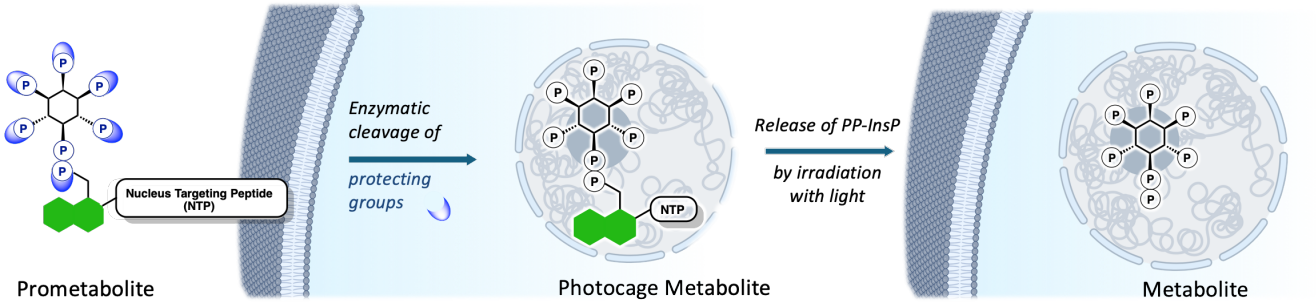
Inositol pyrophosphates (PP-InsPs) are crucial signaling molecules in eukaryotic cells. These highly phosphorylated inositol derivatives play key roles in regulating various cellular processes such as cell proliferation, apoptosis, vesicle trafficking, and ion channel activity to insulin secretion.[1] While PP-InsPs localize predominantly in the cytoplasm, recent studies revealed their presence in the nucleus, suggesting additional nuclear functions for PP-InsPs.[2]

The high turnover between different isomers and the low intracellular concentration of PP-InsPs complicate their study. Therefore, to understand the role of these highly phosphorylated molecules, tools are needed to deliver and manipulate the level of PP-InsPs inside cells. Existing methods are restricted to delivering PP-InsPs to the cytosplasm.[3] Here, we present a novel prometabolite strategy that uses a photocage-protected PP-InsP, allowing for visualization within cells and spatiotemporal control over phosphate turnover. Additionally, we conjugated the modified PP-InsP to a short cationic cell penetration peptide to promote nuclear localization[4] and subsequently released the native form of PP-InsP to investigate its effect in the nucleoli.



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