

Purinosome: Assembly Mechanisms and Biological Functions

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Abstract

Purinosomes serve as metabolons to enhance de novo purine synthesis (DNPS) efficiency through compartmentalizing DNPS enzymes during stressed conditions. Recently, we found that under several purinosome-inducing cues, the expression of ASB11, a substrate adaptor of Cul5 ubiquitin ligase complex, is elevated by epigenetic mechanisms through metabolic or signaling cue. ASB11 in turn mediates a K6-linked polyubiquitination of the DNPS enzyme PAICS at its K74 residue. This ubiquitination facilitates the recruitment of UBAP2, a ubiquitin-binding protein with multiple stretches of intrinsic disordered region, to confer multivalent interactions for triggering liquid-liquid phase separation in vitro and purinosome formation in vivo. Importantly, blockage of purinosome formation impairs DNPS pathway flux under several purinosome-forming conditions. Furthermore, melanoma express high levels of ASB11 to support a constitutive formation of purinosome to which they are addicted for supporting proliferation, viability, and tumorigenesis. This study not only unravels the first mechanism of purinosome assembly and the impacts of purinosome formation in human malignancies, but also provides us with a unique opportunity to decipher the cellular and pathophysiological functions, composition, additional assembly mechanism, and disassembly mechanism of purinosome. I will discuss recent progress in these aspects.