Purinosome fuels mitochondrial DNA and RNA synthesis to mitigate cardiomyopathy

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Purinosomes represent cytoplasmic condensates that compartmentalize *de novo* purine synthesis (DNPS) enzymes to enhance pathway flux. However, the pathophysiological functions of purinosome remain largely unexplored. Here, we report that purinosomes are constitutively formed in cardiac and skeletal muscle cells through a high expression of ASB11, the E3 ligase mediating DNPS enzyme PAICS ubiquitination to drive purinosome assembly. In these mitochondria-rich cells, purinosome-mediated enhancement of purine nucleotide production is preferentially channeled to mitochondria for DNA and RNA synthesis, thereby maintaining mitochondrial OXPHOS activity, dynamics, and redox homeostasis. The selective impact of purinosome on mitochondria is mediated by a purinosome-mitochondrion tethering through Spartin, whose loss-of-function mutations cause Troyer syndrome with mitochondrial and muscle malfunctions. Importantly, *ASB11* is downregulated in the cardiac tissues of cardiomyopathy patients, especially in a cardiomyocyte subpopulation with a feature of enhanced mitochondrial metabolism. Accordingly, purinosome induction or inosine administration mitigates cardiac dysfunction induced by ischemic injury, whereas purinosome depletion aggravates ischemic cardiomyopathy. Our study identifies an unprecedented role of purinosome in supporting mitochondrial functionality to alleviate myocardial injury and highlights a potential therapeutic strategy for treating ischemic cardiomyopathy.