Characterization of mtDNA Release & Innate Immunity upon Mitochondrial Nucleotide Imbalance

Abstract

A variety of mitochondrial molecules have been shown to function as damage associated molecular patterns (DAMPs) which can be recognized by different cellular signalling pathways leading to an inflammatory response. One of these mitochondrial DAMPs is mitochondrial DNA (mtDNA). Recent findings suggest a novel mtDNA release route via mitochondrial derived vesicles (MDVs) upon mitochondrial stress as a mitochondrial quality control pathway (MQC) to maintain mitochondrial fitness. Here we investigated the impact of perturbed mitochondrial nucleotide homeostasis on mtDNA release and innate immunity. We identified mitochondrial nucleotide imbalance, following chemical treatment as well as genetic depletion of i-AAA protease YME1l or mitochondrial exonuclease MGME1, to be novel trigger of mtDNA release via MDVs. Characterizing MGME1 deficiency *in vitro* and *in vivo*, we found that loss of MGME1 induces MDV-mediated mtDNA release, which are subsequentially targeted for extracellular transport via EVs (extracellular vesicles). We elucidate that mtDNA fragments are targeted for extracellular transport upon MGME1 loss rather than whole nucleoids, advancing current studies with a detailed analysis of cytosolically released mtDNA specimen. Moreover, we show that extracellular sequestering of mtDNA fragments upon nucleotide imbalance is sufficient to induce non-cell autonomous innate immunity. These findings indicate that, contrary to previous reports, inflammatory cargo can be engulfed by MDVs and targeted for extracellular transport and highlights the decidedly context specific cargo selectivity of MDVs and EVs. Our work advances the current understanding of mitochondrial nucleotide metabolism and its contribution to mitochondrial function in health and disease and hence defines a novel stressor stimulating MDV shedding. Targeting cellular nucleotide metabolism and MDV-mediated mtDNA release might offer new therapeutic approaches for inflammatory diseases linked to mtDNA involvement, including neurodegenerative diseases and cancer.