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Humanin: a harbinger of mitochondrial-derived peptides?

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Mitochondria have been largely considered as 'end-function' organelles, servicing the cell by producing energy and regulating cell death in response to complex signals. Being cellular entities with vital roles, mitochondria communicate back to the cell and actively engage in determining major cellular policies. These signals, collectively referred to as retrograde signals, are encoded in the nuclear genome or are secondary products of mitochondrial metabolism. Here, we discuss humanin, the first small peptide of a putative set of mitochondrial-derived peptides (MDPs), which exhibits strong cytoprotective actions against various stress and disease models. The study of humanin and other mitochondrial-derived retrograde signal peptides will aid in the identification of genes and peptides with therapeutic and diagnostic potential in treating human diseases.

Mitochondrial biology and function

It is widely accepted that the endosymbiotic origin of mitochondria was from α-proteobacteria that have been engulfed by and integrated into eukaryotic host cells. The incorporation of the mitochondrion (proto-mitochondrion) has changed the course of eukaryotic evolution through a monumental metabolic upgrade by employing oxygen to mass-produce energy and biosynthetic precursors [1]. Owing to their prokaryotic origin, mitochondria are also unique among intracellular organelles in that they contain their own genome. This small genome is thought to be the result of gradual loss or transfer of the great majority of the original bacterial genes to the nucleus, leaving only 13 full-size protein-coding genes that are essential for oxidative phosphorylation. This component of the human genome is beginning to be explored for its potential role in conditions such as aging, cancer, diabetes, deafness, and neurodegeneration [2].

The mitochondrion is responsible for several crucial cellular activities including energy production, regulation of programmed cell death (apoptosis), biosynthetic precursor production, heme synthesis, Fe–S cluster production, ion homeostasis, and reactive oxygen species (ROS) production [3]. Bestowed with such critical responsibilities, it has been known that mitochondria actively participate in determining cellular processes; however, little is understood about how mitochondria transmit information to the host cell. In this article we will discuss a newly emerging concept regarding a novel class of communication conveyed by the mitochondrion to regulate cellular processes and cell fate (Figure 1).

The concept of retrograde signaling from the mitochondrion to the nucleus and beyond

Mitochondria have traditionally been perceived as 'end-function' organelles that receive cellular signals, and in response regulate energy production and apoptosis. However, a coordinated regulation of mitochondrial and nuclear gene expression is critical for cellular homeostasis, which requires constant and active exchange of information [4]. Mitochondrion-initiated communication events that signal and regulate various cellular aspects under normal, stress, and pathological states are referred to *en masse* as retrograde signaling [4], a biological process well conserved from the simple yeast to humans (Figure 1).

To date, a relatively limited number of retrograde signaling molecules and signaling cascades have been explored. Some of the molecules described in this regard are cytochrome *c*, ROS, Ca^{2+}, Fe^{2+}, nitric oxide (NO), and carbon monoxide (CO) [5–7] (Figure 2). Notably, an interesting study in *C. elegans* described non-canonical signals exported from the mitochondria in response to proteotoxic insults [8]. However, these were not peptides encoded within the mitochondria but instead damaged

Glossary

Membrane permeability transition (MPT): an increase in mitochondrial permeability via the formation of a nonspecific pore across the inner mitochondrial membrane, permitting the free distribution of ions and low molecular weight molecules (<1500 Da) across the membrane that can lead to mitochondrial swelling and cell death.
Mitochondrial-derived peptides (MDPs): small peptides that are encoded within the mitochondrial genome in addition to the canonical 13 protein-coding mitochondrial genes.
Nuclear mitochondrial DNA transfer (NUMT): a copy of mitochondrial DNA (mtDNA) that is integrated into the nuclear genome; these are generally considered to be pseudogenes. Also known as nuclear DNA sequences of mitochondrial origin.
Parallel analysis of RNA ends (PARE): a technique that combines 5′-rapid amplification of cDNA ends (RACE) with high-throughput deep sequencing (SBS) and bioinformatics tools that can reveal RNA cleavage sites.
Retrograde signaling: a pathway of communication from the mitochondria to the cell that influences cellular and organismal activities.
Retrograde signaling molecules: these are ions, proteins, and molecules that act as messengers of retrograde signaling (e.g., Ca^{2+}, reactive oxygen species, cytochrome *c*, etc).
tRNA punctuation model: a model describing mitochondrial RNA processing, whereby individual genes are released from a long polycistronic transcript by excising the 22 interspersed tRNAs that are strategically encoded in the mtDNA.

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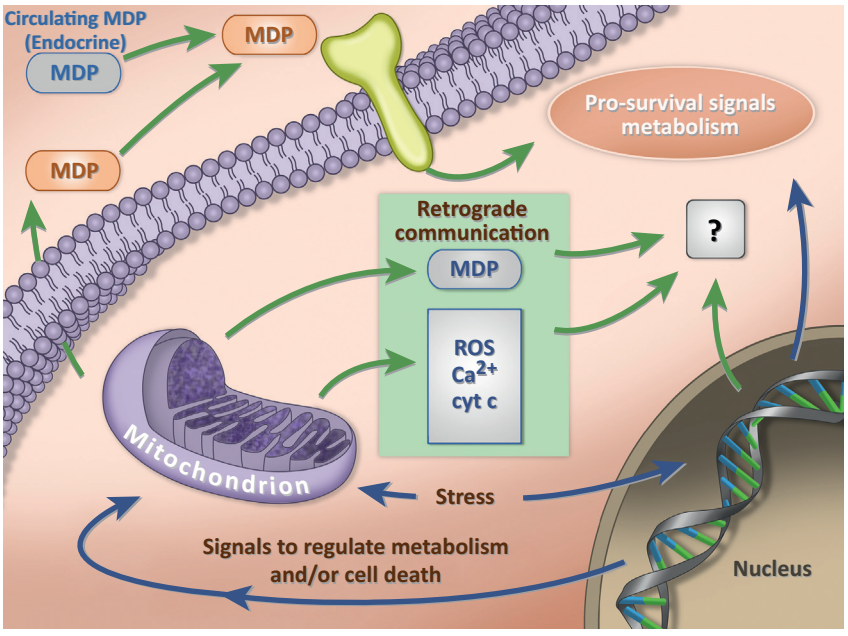

Figure 1. Mitochondrial-derived peptides (MDPs) are retrograde signaling molecules. Mitochondria communicate with the cell through a process largely known as retrograde signaling. Traditionally described means of communication from the mitochondria include Ca^{2+}, cytochrome *c* (cyt c), and reactive oxygen species (ROS). MDPs are recently identified retrograde signals, which are unique in that they are encoded within mitochondrial genome sequences. MDPs such as humanin are thought to act as endocrine as well as intracellular factors with several biological roles in the regulation of cell survival and metabolism.

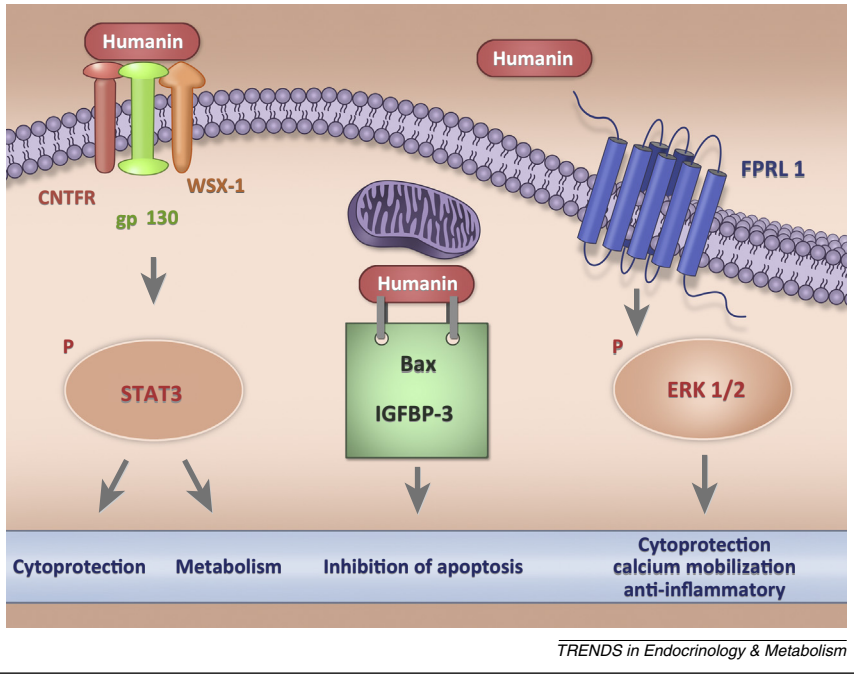

Figure 2. Cellular actions of humanin. Humanin has been shown to possess both intra- and extra-cellular modes of action. Within a cell, humanin interacts with pro-apoptotic proteins such as Bax and IGFBP-3, thereby preventing apoptosis. Extracellular humanin also regulates important cellular processes such as survival, metabolism, and inflammation via two types of cell-surface receptors; a trimeric receptor involving CNTFR/WSX-1/gp130, which relays signals through the STAT3 signaling pathway, and the formyl-peptide receptor-like-1 (FPRL1), which relays signals through the ERK 1/2 signaling cascade. P, phosphorylation.

matrix-protein fragments generated by proteolysis that are encoded in the nuclear genome and imported later into mitochondria. In a way, they are in a comparable class of retrograde signals with cytochrome *c* in that they are nucleus-encoded protein products released back to the cell from the mitochondria. In addition, mitochondrial DNA (mtDNA) itself can act as a signal. A recent study demonstrated that inhibiting autophagy causes mitochondrial dysfunction, and subsequent mtDNA export to the cytosol, via increased mitochondrial membrane permeability transition (MPT; see Glossary), resulting in activation of the caspase-1 inflammasome [9].