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Mitochondria ensure immune surveillance by retro-communication with the nucleus

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Mitochondria cover several functions within the cell, including an influence on the transcription of nuclear genes. Recent work by Tigano et al. (2021) in *Nature* has identified a pathway of mitochondrial retrograde communication in which the nucleus senses aberrations in the mtDNA to drive the innate immune response.

The first rule of hospitality is to ensure guests feel at home. This is rather paradigmatic in the case of mitochondria, which have so successfully integrated into the hosting of eukaryotic cells to the point of defining their homeostasis. The mitochondrion—as we know it—originates from an endosymbiotic engulfment event of an α -proteobacteria by a primordial eukaryotic cell (López-García et al., 2017). Such a critical step in evolution has allowed for the mitochondrion to retain its own DNA, but over time most of the genes encoding for the proteobacterial proteins have been integrated into the nuclear genome. At the same time, the mitochondrion has acquired new components from the hosting cell, expanding its core functions; currently its proteome comprises approximately 1,200 proteins (Kotrys and Szczesny, 2019). The majority of them are transported from the nucleus with the help of an N-terminal mitochondrial targeting sequence (MTS) (Pfanner, 2000), while 13 are encoded by genes (37) contained within the mitochondrial DNA (mtDNA). These translate for all the important components of the electron transport chain (ETC) complexes. Interestingly, the mtDNA also codes for two rRNAs (12S and 16S) and 22 tRNAs to demark an independent capacity for transcription, translation, and replication. Transcription of the mtDNA is driven by a DNA-dependent RNA polymerase known as POLRMT whose activity depends on its association with mitochondrial transcription factor A (TFAM) and mitochondrial transcription factor B2 (TFB2M) (Kotrys and Szczesny, 2019).

The mitochondrial proteome is therefore the result of a fine act of coordination between two genomes that is made possible by a two-way system of communication: (1) nucleus-to-mitochondria (anterograde) and (2) mitochondria-to-nucleus (retrograde) (Jazwinski, 2014). This must endure perturbing events or naturally occurring modifications for which the mito-nuclear feedback signaling is pivotal to guarantee an integrated stress response. Mitochondria are reliable sentinels, and an increasing body of evidence reveals a vast network of driving signals, regulators, and physical tethers that command the retrograde pro-survival communication.

The process of retrograde (RTG) signaling is well characterized in budding yeast, in which it is dependent upon the RTG1–RTG2–RTG3 family of transcription factors that translocate to the nucleus in response to mitochondrial dysfunction, eliciting a transcriptional response. In light of the absent homology of the RTG genes in higher eukaryotes, mitochondrial communication with the nucleus is evidently far more complex, especially in mammals that deploy different executors for various mitochondrial stressors. Those identified, to date, encompass transcription factors (e.g., GPS2, CHOP, SHREB, ATF4, and NF- κ B; Jazwinski, 2014; Cardamone et al., 2018) that rapidly accumulate in the nucleus in response to stress.

The recent work by Sfeir and co-authors enriches the current picture by describing a sensor relay circuit triggered by loss of integrity in the mtDNA (Tigano et al., 2021). The latter is required to preserve mitochondrial function whereby cu-

mulative lesions lead to mtDNA deletion, which is at the basis of varying mitochondrial pathologies. The so-called double-strand breaks of the mtDNA (mtDSBs) are toxic wounds that undermine mitochondrial and hence cellular function. In this elegantly crafted manuscript, the authors show that mtDSBs are a means to drive mitochondrial retrograde signaling. Thus, they demonstrate that mtDSBs are sensed by the nucleus to trigger the innate immune response via phosphorylation of the transcription factor STAT1 and subsequent activation of interferon-stimulated genes (ISGs) (Crosse et al., 2018).

Typically, this takes place following binding of interferon to specific receptors on the cell surface, thus establishing a feedforward mechanism to ensure efficacy of the defensive response. Here, Tigano et al. show that phosphorylation and activation of STAT1 (to boost ISG expression) occur via mitochondrial damage and without the need of interferon (Crosse et al., 2018). mtDSBs, induced by mitochondrial targeted transcription-like effector nucleases (TALENs), trigger herniation of the mitochondrial membranes and release of matrix contents into the cytosol of both DNA and RNA. However, it is the mtRNA to be intercepted by the cytoplasmic dsRNA sensor RIG-I/MAVS, resulting in the nuclear response read by the increase of ISG expression (Figure 1A).

Release of mtDNA and mitochondrial-specific RNA is made possible by macropores formed by the recruitment of the Bcl-2 family members proteins BAX and BAK. Such a requirement for the pathway does not explain the timing of recruitment



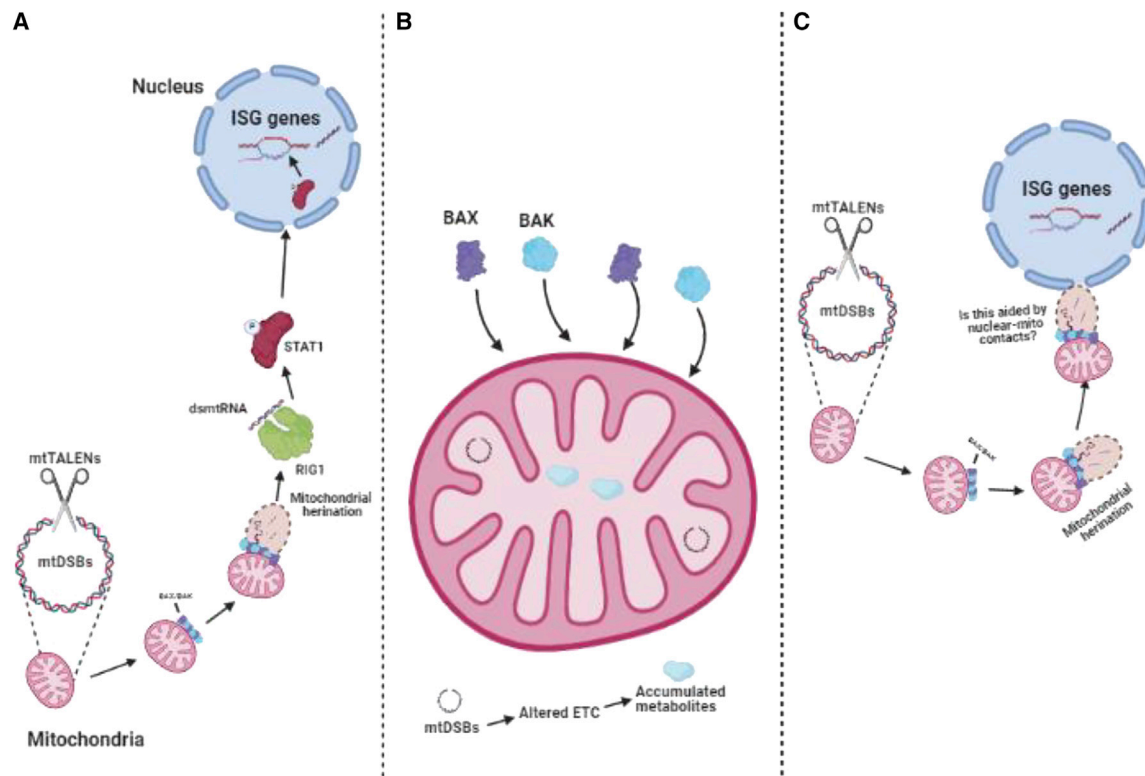


Figure 1. Mitochondrial retrograde response defines innate immune response resembling an ancient interaction

(A) mtDSBs trigger heritation of the mitochondrial membrane and the release of matrix contents into the cytosol through macropores formed by BAX/BAK. Released mtRNA is sensed by the cytoplasmic RNA sensor RIG1, which activates STAT1, leading to its nuclear translocation and the consequent expression of ISGs.

(B) Altered mitochondrial metabolites may recruit and stabilize BAK/BAX on the organelle.

(C) The contact sites between mitochondria and nucleus may aid this pathway of retro-communication. This figure was created with BioRender.

on the mitochondria and which is the signal leading to their stabilization. It is possible that metabolic intermediates are re-routed by the mtDSBs to dock BAX and BAK (Figure 1B), representing therefore the hierarchical step of the process, but further research is required to address this. Far greater is the curiosity to learn why the mtRNA and not the mtDNA is acting as driver of the retrograde signaling. Thus, we do know that extrusion of mtDNA is mediated by BAX/BAK macropores during apoptosis (McArthur et al., 2018), but this seems insufficient to trigger the retrograde response.

We speculate that it is the mtRNA, and not the mtDNA, because the process contributed is an ancient one. RNA is indeed a genetic material that precedes the formation of DNA, likely acting as a reminiscent component of the original interaction (Harris, 2010) between mitochondria and nucleus, thereby suited to reconnect them. In line with retained features across evolution is that the activa-

tion of the innate immune response by mtDSBs resembles a vestige of the ancestral—if not the initial—communication between mitochondria and eukaryotic cells. Proteobacteria may indeed have brought the signaling repertoire for essential immune response once engulfed by the proto-eukaryotic cell, or on the other hand, the cells could have searched for those exogenous elements as a shield during precariousness. Recent research has identified the presence of physical mito-nuclear interactions (Desai et al., 2020) forming during stress. This raises the question of whether this mitochondrial feedback signaling mediated by the mtRNA is facilitated by specific contact sites with the nucleus to empower surveillance and hence protect from danger (Figure 1C).

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DECLARATION OF INTERESTS

The authors declare no competing interests.

REFERENCES

- Cardamone, M.D., Tanasa, B., Cederquist, C.T., Huang, J., Mahdavi, K., Li, W., Rosenfeld, M.G., Liesa, M., and Perissi, V. (2018). Mitochondrial retrograde signaling in mammals is mediated by the transcriptional cofactor GPS2 via direct mitochondria-to-nucleus translocation. *Mol. Cell* 69, 757–772.e7.
- Crosse, K.M., Monson, E.A., Beard, M.R., and Helbig, K.J. (2018). Interferon-stimulated genes as enhancers of antiviral innate immune signaling. *J. Innate Immun.* 10, 85–93.
- Desai, R., East, D.A., Hardy, L., Faccenda, D., Rigon, M., Crosby, J., Alvarez, M.S., Singh, A., Mainenti, M., Hussey, L.K., et al. (2020). Mitochondria form contact sites with the nucleus to couple prosurvival retrograde response. *Sci. Adv.* 6, eabc9955.

Harris, T. (2010). Evidence for RNA origins. *Nature* 464, 494.

Jazwinski, S.M. (2014). The retrograde response: a conserved compensatory reaction to damage from within and from without. *Prog. Mol. Biol. Transl. Sci.* 127, 133–154.

Kotrys, A.V., and Szczesny, R.J. (2019). Mitochondrial gene expression and beyond-novel aspects of cellular physiology. *Cells* 9, 17.

López-García, P., Eme, L., and Moreira, D. (2017). Symbiosis in eukaryotic evolution. *J. Theor. Biol.* 434, 20–33.

McArthur, K., Whitehead, L.W., Heddleston, J.M., Li, L., Padman, B.S., Oorschot, V., Geoghegan, N.D., Chappaz, S., Davidson, S., San Chin, H., et al. (2018). BAK/BAX macrophages facilitate mitochondrial herniation and

mtDNA efflux during apoptosis. *Science* 359, eaao6047.

Pfanner, N. (2000). Protein sorting: recognizing mitochondrial presequences. *Curr. Biol.* 10, R412–R415.

Tigano, M., Vargas, D.C., Tremblay-Belzile, S., Fu, Y., and Sfeir, A. (2021). Nuclear sensing of breaks in mitochondrial DNA enhances immune surveillance. *Nature* 591, 477–481.

Midlobular zone 2 hepatocytes: A gatekeeper of liver homeostasis

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The liver consists of different zones that vary in function depending on their lobular localization. It remained unclear which zone serves as a source of repopulating/regenerating hepatocytes; however, experiments by Wei et al. (2021) in 11 *CreER* knockin murine strains revealed a vital role for zone 2 hepatocytes in liver homeostasis.

The liver, which consists of lobules, is known to have distinct zones that vary in function depending on their lobular localization (Jungermann, 1992). For example, the hepatocytes in the peri-portal zone are responsible for several processes, such as gluconeogenesis, fatty acid β oxidation, cholesterol synthesis, and ammonia metabolism, while those in the peri-central zone are mainly responsible for glycolysis, drug metabolism and detoxification, and fatty acid synthesis (Kietzmann, 2017). Furthermore, this hepatic zonation is shown to be closely associated with fatty liver disease in obesity-associated type 2 diabetes (Kubota et al., 2016).

It has been shown by single-molecule fluorescence *in situ* hybridization (smFISH) that the liver is divided into 9 lobular layers from the central to the portal veins, while single-cell RNA sequencing showed that the hepatic enzymes required for biosynthesis of bile acid are collaterally expressed from the central to the portal veins (Halpern et al., 2017).

These findings showed that hepatocytes vary in their function depending on which zone they belong to. Further, previous studies using mice deficient in leucine-rich repeat-containing G protein-coupled receptor (LGR) 4/5 showed that liver zonation is mediated by Wnt/ β -catenin signaling in the context of an R-spondin (RSPO)-LGR 4/5-zinc and ring finger 3 (ZNF3)/ring finger 43 (RNF43) axis (Benhamouche et al., 2006; Planas-Paz et al., 2016). Further, Wnt is secreted from vascular endothelial cells in the pericentral zone to direct hepatic zonation and is also implicated in hepatocyte self-repair mechanisms (Wang et al., 2015). However, it remained unclear which zone serves as a source for repopulating or regenerating hepatocytes.

To address this challenging issue, Wei et al. generated 11 murine strains with knockin *CreER* whose Tomato protein expression is tamoxifen-inducible in varying patterns from zones 1 to 3 to visually compare the protein expression between these strains (Wei et al., 2021).

A close examination of Gls2, which was shown to be evenly expressed in zone 1, showed a gradual decrease in the proportion of Gls2-positive hepatocytes after treatment with tamoxifen during the course of the study, suggesting that zone 1 hepatocytes are least likely to play a role in hepatocyte self-repair mechanisms. In contrast, an examination of hepatocytes using Cyp1a2, which was shown to be expressed in zones 2 and 3, but not in zone 1, showed a gradual increase in expression over time in the proportion of Cyp1a2-positive cells, exactly where that of Gls2-positive cells was shown to be decreased. A further examination of hepatocytes using Arg1.2, which was shown to be expressed in zones 1 and 2, showed an increased expression in zone 3 over time, demonstrating that zone 2 hepatocytes are responsible for the self-repair of hepatocytes in zones 1 and 3. Indeed, observation of hepatocyte proliferation using Arg1.2 and Cyp1a2 along with 5-ethynyl-2'-deoxyuridine (EdU) staining

