# Free range mitochondria are coming for you

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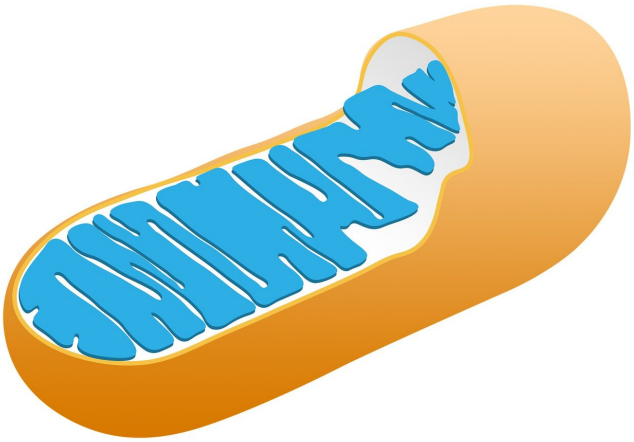

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Transfer of mitochondria between cells is a ubiquitously occurring and now universally known phenomenon. For years, researchers have been serially demonstrating that one particular new cell type can transfer its mitos to yet another particular cell type to achieve some specific metabolic goal essential to survival of the meta-host organism. But what happens when the mitochondria come from the outside world, from other members of your own species, or from a different species altogether? In addressing this very real situation, we first must look at the particulars of how and why mitos are transmitted across cell boundaries in the first place.

One of the latest dispatches, coming to us courtesy of *EMBO Reports*, describes a curious situation in which mesenchymal stem cells (MSCs) transfer mitos directly to T cells in order to tamp down an overactive immune system and curb an inflammatory response. More specifically, the Chilean authors report that mito uptake by CD+ T cells induces regulatory T cell differentiation and activation through increased expression of FOXP3, IL2RA, CTLA4, and TGFb mRNAs. Mesenchymal stem cell transfer had been well established in earlier disease models of acute respiratory distress (ARDs), in which transfer to macrophages through tunneling nanotubes upregulates their phagocytic capability.

Similarly, intratracheal administration of MSCs resulted in transfer of mitos to the alveolar epithelium to boost metabolic activity and mitigate lung damage. Other research has shown that bronchoalveolar fluid normally contains many mitos encapsulated in extracellular vesicles, and that myeloid-derived regulatory cells transfer mitos to CD4+ T cells using these exosomes. The donated mitos then integrate directly with the T cell mitochondrial network syncytium, suggesting some tantalizing possibilities for treating inflammation in the lungs.

Could we be talking about a potential new way to treat Covid-19 induced respiratory distress, here?

Fixing ARD by simply inhaling mitos may sound like a dream, but it is perhaps something worth looking into a bit more. The key is understanding how the mitos actually travel. In other words, what are the mitochondrial circuits? Many clues have recently emerged, including what mitos are capable of doing when they cycle through the master of all networks—the nervous system. The one-way travel to macrophages described above does not necessarily end there. Macrophages can, in turn, donate their mitos directly to nerve endings in times of need. Once there, they can do some incredible things. For example, in sensory neurons of the DRG (dorsal root ganglion) mitos ultimately derived from M2 macrophages turn off the inflammation response and completely resolve the associated pain messaging. This leg of the circuit requires expression of CD200 Receptor (CD200R) on macrophages and the non canonical CD200R-ligand iSec1 on sensory neurons.

Perhaps even more intriguingly, these mitos also have a side-hussle—they briefly sojorn as free range mitochondria in whole blood. During these sabbaticals, they persist entirely cell free, but still respiratory competent mitochondria. What this essentially means is that when we donate and receive blood or bone, we are also exchanging not just mitochondria, but also in a very real genetic sense, our identities—at least as defined within the limits of current forensic testing of this mosaic-chimeric state. No one should be all that surprised, because our species is also on the cusp of being actively engaged in a subtle but perhaps more insidious trans-species mitochondrial migration through organ transplant.

I recently spoke with Alain Thierry, corresponding author on the whole blood mito paper about the implications of the potentially massive invasive heteroplasmy that might be incurred after routine blood transfusion. In particular, when such an event might be beneficial and when it might not, and how to prove it. I received a nice response: "I am working on this, and it is difficult for me to divulge it, every researcher would say the same. Your question is very relevant."

One tangible prospect emerges from Chinese researchers who have used mitotherapy to improve cognitive and motor performance in aged mice. Their results showed that the heterozygous mitochondrial DNA of both aged and young mice coexisted in several tissues shortly after intravenous injection of young mitos. It is interesting that the most susceptible population for Covid-19 are the elderly, precisely those with the highest probability of age-associated mitochondrial dysfunction. Furthermore, there have been a number of young people that have succumbed to Covid-19.

Considering all this, it would be a worthwhile pursuit to look more closely at the genetics of these unfortunate individuals to determine if, in fact, the afflicted younger people are genetically predisposed to subclinical mitochondrial deficiencies, and might benefit from some novel interventions as mentioned here.

**More information:** Angela C Court et al. Mitochondrial transfer from MSCs to T cells induces Treg differentiation and restricts inflammatory response, *EMBO reports* (2020). DOI: 10.15252/embr.201948052