Abl2 kinase phosphorylates bi-organellar regulator MNRR1 in mitochondria, stimulating respiration

The mitochondria are the well-known “powerhouse” of the cell. Not surprisingly, its functional state is important to other parts of the cell and, conversely, information about the needs of other parts of the cell help determine mitochondrial function. Consequently, as is increasingly being appreciated, two-way communication takes place between the mitochondria and other organelles, in particular between the mitochondria and the nucleus. The latter is known as retrograde regulation and the pathways by which it occurs are of considerable current interest.

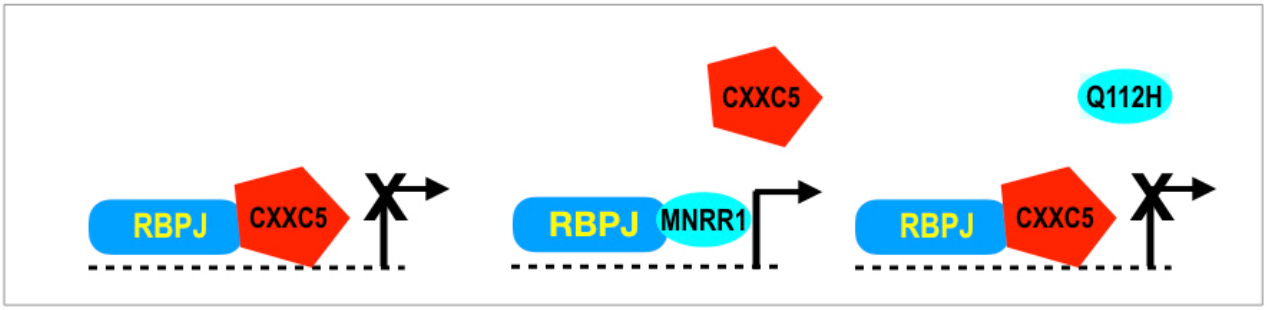

Fig. 1. Model for events at the ORE. CXXC5 is shown repressing transcription in the absence of MNRR1 (left), being displaced by MNRR1 when sufficient amounts are present (center), and unable to be displaced by MNRR1 containing the Q112H mutation (right).

One such pathway involves the mitochondrial intermembrane space protein MNRR1 (also called CHCHD2, AAG10) that we have been studying, and its paralog, CHCHD10. Both of these are mitochondrial proteins…, and nuclear proteins. In the case of MNRR1, we know that it binds to the terminal complex of the electron transport chain, cytochrome *c* oxidase (COX), and we hypothesize that it binds near the site where cytochrome *c* docks to transfer the electrons it picked up further upstream in the chain; furthermore, that such MNRR1 binding stimulates mitochondrial metabolism by facilitating this docking and transfer.

We discovered a second layer in the mitochondrial regulation by MNRR1: it needs to be phosphorylated to bind well to COX. Phosphorylation takes place on one of the two tyrosine amino acids in the protein, at position 99 in the human protein. Furthermore, we discovered the kinase that carries out the phosphorylation in mitochondria: it is Abl2 kinase, also called ARG.

When phosphorylated MNRR1 binds to COX, mitochondrial respiration increases and mitochondria take on a more elongated, networked appearance typical of healthier cells. Conversely, depleting cells of MNRR1 causes a reduction in respiration, a slowing of growth, an increase in damaging

reactive oxygen species (ROS) levels, and a more fragmented appearance of mitochondria.

Strikingly, in addition to the mitochondrial function of MNRR1 described above, MNRR1 also functions in the nucleus as a transcription factor. It does so by promoting the transcription of genes that contain a 13-base pair promoter element that we call the oxygen responsive element or ORE by a process that involves assembling with other proteins on the ORE. The oxygen responsiveness refers to the increased amount of MNRR1 and of other genes that contain a promoter ORE that is synthesized at 4% oxygen compared to at both higher and lower oxygen concentrations. Many of the genes promoted by MNRR1 function in mitochondria and are stress related such as superoxide dismutase.

A protein changing mutation (Q112H) has been found in a family that additionally has members with Charcot-Marie-Tooth disease (CMT), a peripheral neuropathy that can have multiple causes; in this family it is caused by a duplication of the gene PMP22. The mutation in MNRR1 appears to cause a more severe disease presentation. When the mutation is studied in cultured cells, it reduces MNRR1 function in both the nucleus and the mitochondria; furthermore, cells become less resilient to stress. For example, ATP content declines sharply after starvation that is brief enough that no measurable effect is seen in cells containing the normal form of MNRR1.

In conclusion, MNRR1 and CHCHD10 are proteins that function in two compartments of the cell, the mitochondria and the nucleus. As communicators between the two organelles they adjust energy metabolism at the gene and enzyme level to environmental cues such as changes in oxygen concentration or stress. These are crucial regulatory mechanisms allowing the cell and ultimately the entire organism to adapt to the ever-changing conditions they are facing.

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