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SPOTLIGHT

Sense and sensibility: ATM oxygen stress signaling manages brain cell energetics

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The ataxia-telangiectasia mutated (ATM) gene regulates DNA damage repair, oxidative stress, and mitochondrial processes. In this issue, Chow et al. (2019. *J. Cell Biol.* https://doi.org/10.1083/jcb.201806197) connects ATM's oxidative stress response functions to the sensing of metabolic ATP energetics distinctively important in high energy–demanding Purkinje brain cells, which could explain the most distinct A-T patient feature, cerebellar ataxia.

Ataxia-telangiectasia (A-T) is a rare neurodegenerative disease that results in poor coordination, a weakened immune system, and a high likelihood of developing cancer (1). Mutations in the ATM gene, short for "ataxia-telangiectasia mutated," results in the loss of a subset of brain cells called Purkinje cells, which signal to the part of the brain that controls movement in the cerebellar cortex. Thus, their degeneration causes ataxia, which is a loss of voluntary muscle movement.

ATM is most prominently studied for its molecular roles in the nucleus, where it senses damaged and broken DNA molecules (2) and then signals and coordinates their repair. ATM is a kinase, an enzyme that adds posttranslational modifications in the form of a phosphate group on other proteins, including the tumor suppressor p53, to start a signal cascade that ultimately can result in cell cycle arrest, recruitment of other DNA repair factors, and/or induced cell death. When ATM is mutated, additional DNA mutations and DNA abnormalities arise from unrepaired DNA. Yet, cells may be unhalted and continue to proceed through the cell cycle. Both features are associated with cancer development. Indeed, A-T patients have a cancer risk 37–100 times higher than the normal population. So, ATM's role in DNA repair can credibly explain why A-T patients are susceptible to cancer. However, the most striking patient feature typically preceding cancer is ataxia. This is a state where the cells in question, which are postmitotic, do not go through a cell cycle, and ATM's DNA repair and related cell cycle arrest functions logically appear largely irrelevant at first glance. How mutations in ATM cause the cell death of Purkinje cells in the brain therefore remained a mystery.

A cytoplasmatic role for ATM in mouse neurons was first reported by Wynshaw-Boris nearly two decades ago (3). A milestone finding by the Paull laboratory described a cytosolic DNA repair–independent role of ATM that defined the protein as a redox sensor (4): in the presence of reactive oxygen species (ROS), ATM can add phosphate groups onto itself, which initiates two ATM proteins binding to each other, whereby this dimeric protein complex is activated for phosphate additions onto other proteins and so for downstream protein player activation. The Gatti (5), Shadel (6), and Kastan (7) laboratories further linked ATM outside of the nucleus directly to mitochondria and proper mitochondrial homeostasis (7).

Mitochondria are the power houses of the cell: organelles that are the physical location for ATP production, which is the cell's fuel. In this rigorous study, Chow et al. creatively amalgamate the distinct energy needs of Purkinje brain cells with these lesser understood ATM functions in oxygen sensing and in mitochondria to elucidate a molecular mechanism that can logically explain the mysterious ataxia phenotypes and define a so far unappreciated ATM sensor of, and responder to, the cell's energy requirements (8).

Specifically, Purkinje cells in the cerebellum have an acute and extraordinarily high demand for ATP during nerve signaling. Chow et al. show that A-T patient cells are restricted in their oxidative respiration potential in the mitochondria, the predominant cellular process resulting in ATP production (8). Thus, when energy demands are high, such as during nerve activation, the potential for ATP production in A-T patient neurons is not sufficient to meet these needs, and this lack in ATP energetics is associated with the death of these cells. Elegantly, the authors establish that acute ATP demand imbalances the oxidative respiration machinery and so causes elevated ROS molecules. These ROS then activate ATM, consistent with ATM's role as a redox and oxidative stress sensor, where oxidation of ATM causes dimerization, autophosphorylation, and ATM kinase activation for phosphorylation and activation of downstream protein (Fig. 1). As Chow et al. show, this includes NRF1, which, when phosphorylated by ATM, translocates into the nucleus, where it in turn promotes the transcription of nuclear-encoded respiration proteins (8). Importantly, an NRF1 mutant protein that mimics phosphorylation by ATM can rescue the ATP production potential in A-T cells, confirming that dysregulated energetics of A-T cells, at least in part,

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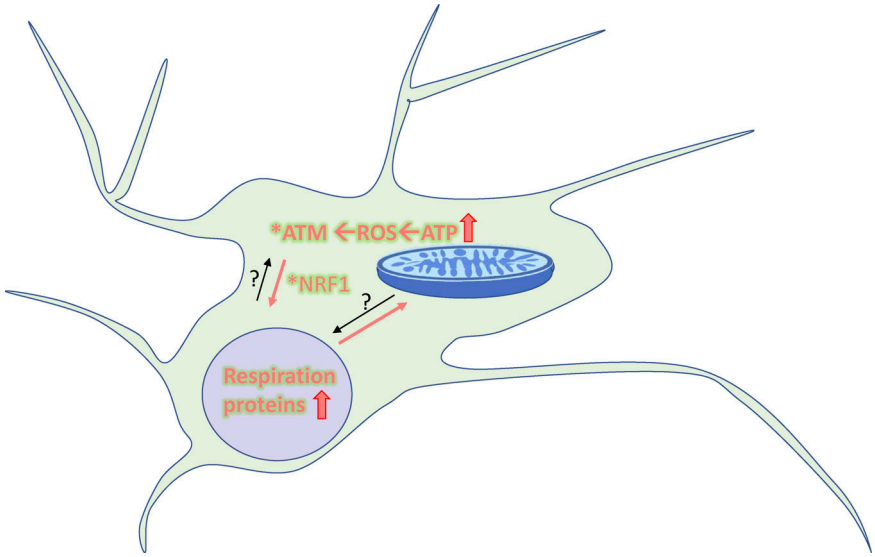

Figure 1. **Chow et al. define a new role for ATM in sensing the high cellular ATP demands of Purkinje brain cells by ROS and responding by activating (*) the NRF1-dependent transcription of nuclear-encoded respiration proteins necessary for ATP production in the mitochondria.** Remaining questions (?) include how ATM's separable roles in the mitochondria (blue), the cytosol (green), and the nucleus (purple) during DNA repair, oxygen sensing, and mitochondrial processes are working in concert for suppression of the diverse A-T patient phenotypes including cancer and cell death.

depends on ATM regulation of NRF1. Consistent with the proposed requirement for increased ATP in Purkinje cells, these brain cells express particularly high levels of NRF1. Thus, the inability of A-T cells to induce NRF1-dependent ATP metabolics when needed can fittingly explain the selective death of Purkinje cells in A-T patients. The authors demonstrate that this ATM role is distinct from its role during DNA repair.

This study thus freshly defines ATM functions as a "metabolic damage sensor," extending the repertoire of the solidifying concept that established ROS as a signaling molecule (4, 9). With the striking dependence of Purkinje cells on ATM's role as an energy regulator, this study intriguingly provides a compelling explanation for the most pronounced biological effect of ATM deficiency: ataxia.

Yet, A-T patients are cancer prone. For disease understanding, it is critical to discern the molecular reactions that are inactivated by the disease-causing gene mutations. In many cases, a gene is important for multiple cellular processes, which can be genetically separated, such as is the case for ATM. The question arising in moving forward is how these separable functions connect to each other for one comprehensive cellular purpose. In the nucleus, ATM is regulated by the repair nuclease MRE11 and in turn regulates MRE11 nuclease activity. Mutations in MRE11 also lead to the ataxia-like disorders (ATLDs), suggesting that it is a common function shared between MRE11 and ATM that is distorted in ataxia pathology. Deregulation of MRE11 nuclease activities indeed shifts DNA repair from error-free break repair to end-joining repair by micro-homology (10), a process that is obligatorily mutagenic and is a repair pathway that is also active in postmitotic cells such as neurons. Thus, ATM's and MRE11's overlapping DNA repair function in principle may also contribute to brain cell death in addition to the here identified ATM roles in ATP energetics. In support of this, a mutant MRE11, found in an ATLD patient presenting with ataxia and cancer, remains proficient for ATM activation, yet is distorted in MRE11 nuclease activity and DNA repair (11). So, the ataxia in this patient cannot readily be explained by NRF1 and ATP regulation at the MRE11–ATM axis alone, but suggests that distortion of postmitotic DNA repair may also contribute. Nevertheless, it will be interesting to test MRE11 functions on ATP energetics in neurons.

A consequence of altered metabolic enzyme expression in A-T cells, among others, is a preference for pyruvate conversion to lactate over utilization of the Krebs cycle in the mitochondria. As a consequence, Chow et al. show that the first metabolite levels of the Krebs cycle, including isocitrate, are low in A-T cells (8).

While the primary purpose of the Krebs cycle is to provide the electrons necessary during ATP production by the respiratory chain, it also generates metabolites important for reactions outside the mitochondria: citrate is the substrate for acetyl-CoA production in the cytosol, which in turn is required for chromatin acetylation, a powerful signaling and regulation process during DNA repair. As such, defects in ACLY function, the enzyme converting citrate to acetyl-CoA, result in reduced chromatin acetylation in the nucleus and less recruitment of repair factors, including BRCA1, and therefore less repair of broken DNA (12). Thus, even though ATM's roles in ATP energy sensing are experimentally separable from its role during DNA repair, they still could affect and relate to each other on multiple levels. In this case, reduced NRF1 activation could result in reduced acetyl-CoA levels that indirectly, and independent of ATM's direct role at sites of DNA breaks, cause DNA repair defects by insufficient BRCA1 recruitment.

The connection of cytosolic ATM activation and mitochondrial ROS has recently been established by the Shadel group, who showed another facet of ATM metabolic regulation (13): ATM promotes glucose flux through the pentose phosphate pathway, which in turn increases cellular antioxidant capacity and so increases the cell's damage defense and prevention. The newly added ATM functions for control of cellular energetics by NRF1-dependent transcription regulation highlight the keystone hub function of ATM in cellular stress "sense and

sensibility," where ATM senses a multitude of stress sources, including DNA damage, oxidative stress, and energetic stress. As a reaction to any of these stresses, ATM then "sensibly" regulates the cellular responses to adequately address them.

More generally, this study illuminates the insight that, in pleiotropic diseases such as A-T, the Anna Karenina principle often applies, where active ATM function is required for all cells to be happy, but when ATM is defective, different cells are unhappy in their unique way. In Purkinje cells, it appears that ATM's energy-sensing role could be surpassing all others. The acute requirement for vast amounts of ATP leads to cell death if not fulfilled. In other cell types, including blood cells, ATM deficiency causes cancer likely due to loss of its DNA repair function, its energy regulation function possibly indirectly regulating DNA damage repair, its oxidative stress-sensing function, or all of the above. It will be important to gain a better understanding of this in future studies. ATM's diverse functions are separable on a molecular level. This not only allows, but likely demands, that different aspects of the A-T disease require targeting by different means, simultaneously providing new opportunities as well as complexity and challenges for future treatment strategies.

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