

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 unaltered 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 cytoplasmic 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

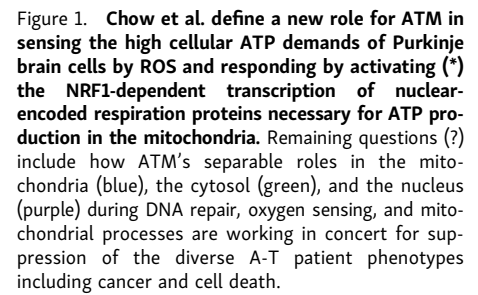
phenotypes and define a so far unappreciated ATM sensor of, and responder to, the cell's energy requirements (8).

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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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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