AATF: A new actor in the complex world of mTOR

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Reflecting the pivotal role of mammalian target of rapamycin (mTOR) in the cell, a number of pathways, several of which exhibit changes in expression or activity in different cancers, tightly control its activation. We have recently demonstrated that antiapoptotic transcription factor (AATF) regulates mTOR in response to several kinds of stress.

Mammalian target of rapamycin (mTOR) is a highly conserved serine/threonine kinase that plays a central role in cell homeostasis, regulation of cell growth, metabolism, and autophagy in response to different environmental conditions.¹ Its relevance is also demonstrated by the involvement of deregulation of the mTOR pathway in several diseases including cancer, type 2 diabetes, and obesity. mTOR participates in 2 distinct functional complexes, mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2). mTORC1 is a regulator of cell growth and protein translation, whereas mTORC2 controls the actin cytoskeleton and cell survival by phosphorylating important substrates such as AKT1 and SGK1. Both protein complexes are closely controlled by numerous feedback mechanisms that activate or repress mTOR in response to different intra- and extracellular stimuli. Notably, many stress conditions such as energy deprivation or low oxygen levels inhibit mTORC1 activity through several mechanisms, indicating that this pathway plays an important role in adaptation to many types of stress.² Moreover, several pieces of evidence indicate that tumor protein TP53 (best known as p53) controls mTOR activity in response to DNA damage by mediating the transactivation of

several negative regulators of mTOR.² Recently, we have described the protein antiapoptotic transcription factor (AATF, also known as CHE1) as a new and important regulator of mTOR activity in response to stress.³

AATF is a transcriptional cofactor that is involved in the regulation of gene expression by connecting specific transcription factors to the general transcriptional machinery.⁴ This protein has strong antiapoptotic activity and is implicated in several cellular pathways, regulating proliferation and survival in both physiologic and pathologic conditions. In response to DNA damage, AATF undergoes several post-translational modifications that influence its localization, half-life, and interacting partners. In particular, the checkpoint kinases MAPKAPK2, ATM, and CHEK2 phosphorylate and activate this protein.^{5,6} These modifications induce translocation of AATF from the cytoplasm to the nucleus, lead to AATF stabilization and accumulation by increasing its resistance to proteasome degradation, and transfer this protein from pathways regulating cell cycle progression to those involved in cell cycle arrest and survival.^{5,6}

In our recent study we demonstrate that AATF is activated by checkpoint kinases not only when DNA damage is present, but also in response to other kinds of stress such as hypoxia and glucose deprivation. Once activated, AATF controls mTORC1 and mTORC2 activities by inducing expression of *DDIT4* and *Dep-1*, 2 important inhibitors of mTOR. Indeed, phosphorylated AATF shows increased levels at *DDIT4* and *Dep-1* promoters and AATF expression is required for the activation of these genes in response to cellular stress. These results identify a novel mechanism by which p53-independent activity of mTOR is

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Figure 1. A possible model to explain the involvement of AATF in mTOR pathway. In response to cellular stress, antiapoptotic transcription factor (AATF) is activated and recruited onto *DDIT4* and *Deptor* promoters, inducing their expression. This results in a simultaneous decrease in mTORC1 activity and increase in mTORC2 activity, allowing induction of autophagy and survival.

controlled in response to stress, and although *DDIT4* was already been known to be induced by several stresses *Deptor* was newly identified as another gene that is modulated in response to cellular damage. It is interesting to note that AATF overexpression strongly induced mTORC2 activity, probably through the inhibition of mTORC1 and a shift in the balance between the 2 complexes.

In this study AATF was found to play a role in autophagy induction by regulating the activity of mTOR signaling, a central regulator of this pathway.⁷ Autophagy is a tightly regulated pathway by which cells can survive in the presence of several stressors, and many associated molecular events indicate a mutual exclusion

between autophagy and apoptosis.⁸ Therefore, these results allow us to propose a model in which AATF is an important regulator of the balance between autophagy and apoptosis in response to cellular stress whereby, once activated, AATF promotes cell cycle arrest and survival and inhibits the activation of apoptosis. At the same time, AATF may contribute to prevention of an energy crisis under stress conditions by maintaining low mTORC1 activity and high mTORC2 activity, thus reducing energy consumption while promoting energy production.

Deptor has been reported to be overexpressed in a particular subset of human multiple myelomas (MMs) in which it is

required to sustain AKT1 activation and cell survival, most likely by relieving a negative feedback loop induced by mTORC1.⁹ Consistent with the control of *Deptor* expression by AATF, analysis of 559 MMs from a specific dataset revealed a linear correlation between *AATF* and *Deptor* mRNA expression. These data were further confirmed by analysis of AATF and *Deptor* expression in 120 human primary MM samples. This analysis revealed almost undetectable AATF and *Deptor* protein expression levels in monoclonal gammopathies samples; however, expression levels increased in smoldering and symptomatic myeloma samples, leading us to hypothesize that these proteins play an important role

during the progression of this disease. Of note, autophagy levels in MM samples strongly correlated with AATF and Dep-
tor expression. Because of the increased demands of dealing with immunoglobulins within the endoplasmatic reticulum, MM cells heavily depend on the ubiquitin-proteasome and the unfolded protein response (UPR) pathways for survival. The induction of autophagy is an additional mechanism that protects MM cells, and basal levels of autophagy are physiologically required in normal plasma cells.¹⁰ Therefore, MM cells may inherit the autophagy dependence of normal plasma cells, and may also induce autophagy through UPR. Consistent with this notion, AATF has been shown to protect cells from the UPR,⁴ and its depletion in primary cells from patients with symptomatic myeloma results in a decrease in autophagy induction with a concomitant increased rate of apoptosis. These results support a model in which the high levels of AATF and Dep-
tor observed in patients with MM not only ensure high levels of

AKT1 activity, but also support the autophagic pathway and survival of these cells (Fig. 1). Additional studies are obviously required to further validate this hypothesis and confirm AATF as a putative target for the treatment of this disease.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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