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Cell Type-Dependent Function of ATF5: Where We Go from Here

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Uncontrollable cell proliferation and suppressed apoptosis are hallmarks of tumorigenic transformation [1-3]. Deregulation of genes controlling cell proliferation and survival plays an important role in the process. For instance, apoptotic genes are frequently down-regulated while anti-apoptotic genes are highly expressed in a number of cancer cell types; artificial down regulation of anti-apoptotic genes or up regulation of apoptotic genes are often sufficient to eradicate those cancer cells. The activating transcription factor 5 (ATF5 or ATFx) is a member of the ATF/CREB transcription factor family. Although ATF5 is known to regulate cell cycle progression [4-7], cell survival [5-13], autophagy [14], cell fate determination [15-17] and cellular stress response [13-19], and it is likely involved in the development of schizophrenia [20-22] and chronic lymphocytic leukemia [23], only a few of its targets have been reported and the mechanism of ATF5 function remains largely unknown and occasionally controversial.

Previous reports have shown that ATF5 enhances cell survival and proliferation of glioma, breast cancer cells and neuroprogenitor cells [5,10-12,24] while eliciting a G2/M blockade in hepatocellular carcinoma cells [4,6]. ATF5 acts as a pro-survival factor in HeLa and hematopoietic FL5.12 cells [8] but may also increase cisplatin-induced apoptosis through up-regulation of cyclin D3 in HeLa cells [25]. Transactivation of Mcl-1 by ATF5 was found to be essential for the survival of GL261 glioma cells [9] but Bcl-2 was instead activated by ATF5 in C6 glioma and MCF-7 breast cancer cells [11]. ATF5 is essential for the survival of HeLa [8], glioma [5,10,11,24], and breast cancer cells [5,11,12], but seems to be dispensable in HEK293, PC12, astrocytes, mouse embryonic stem cells and breast epithelial cells [11,15,16]. ATF5 expression blocks neuronal and glial differentiation of neuroprogenitor cells [15-17] while promoting intestinal differentiation of the Caco-2 cells [26]. These findings highlight the cell type-dependent function of ATF5.

ATF5 may interact with several distinct DNA regulatory elements to modulate the expression of genes whose promoters contain them. It suppresses CREB-responsive element (CRE)-dependent gene transcription [6,15] but activates amino acid responsive element (AARE)-dependent gene transcription [18,27]. We found that ATF5 can also recognize an ATF5-specific responsive element (ARE) and stimulate ARE-containing promoters [5,11,28]. Significant downstream targets known to be regulated by ATF5 include stress-related genes asparagine synthase [29,30], CHOP [18], CYP2B6 [31], HSP27 [32]; apoptotic regulators Mcl-1 [9] and Bcl-2 [11]; and cell proliferation regulators Egr-1 [5] and ID1 [4].

ATF5 expression is induced in response to various forms of cellular stress including Endoplasmic Reticulum (ER) stress [33,34], arsenite exposure [18,34], and amino acid limitation [18,27], among others. ATF5 is known to subject to multilayered regulation that includes transcriptional regulation by EBF1 [35], translational regulation that is controlled by phosphorylated eIF2 [19,34], and post-translational regulation that involves phosphorylation [26], acetylation [5], and ubiquitin-mediated [6,7,13,36,37] and caspase-mediated proteolysis [6,13]. We found that ATF5 is an extremely unstable protein with a half-life of about 1 h in HeLa, C6 and MCF-7 cells and that both chaperone proteins HSP70 and NPM1 are involved in regulating ATF5 protein stability [6,13].

Concluding Remarks

Current research indicates that ATF5 plays important roles in diverse biological processes including cell proliferation, cell survival, cellular stress response, cell fate determination, and is involved in the development of several human diseases such as cancer and neurological disorders. Our understanding of the mechanism by which ATF5 functions is very limited and many questions remain unanswered. There are a number of urgent questions need to be addressed. For instance, what are the causes for the seemingly varied and sometimes opposing effects exerted by ATF5 in different cell types? How is ATF5 involved in so many critical biological functions while at the same time it displays remarkable cell type-dependent regulation? Are there more vital downstream transcriptional targets of ATF5 that have yet to be discovered? Only a few binding partners have been identified for ATF5, are there others that hold the secrets of ATF5 function? Although we had found that ATF5 acetylation of K29 affects ATF5 interaction with p300 and the transcriptional activity of ATF5 [5], are there other post-translational modifications on ATF5, such as phosphorylation and glycosylation, that may regulate ATF5 function? Under what conditions are these modifications critical? With the increasing pace of the ATF5 research, we can anticipate significant progress in answering these important questions in the next few years. These advances will not only elevate our understanding of the mechanism by which ATF5 function but also help uncover novel therapeutic targets for the treatment of the various human diseases in which ATF5 plays a role.

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