CELL CYCLE
2016, VOL. 15, NO. 11, 1401–1402
http://dx.doi.org/10.1080/15384101.2016.1168200

Taylor & Francis
Taylor & Francis Group

CELL CYCLE NEWS AND VIEWS

Yin and yang of 4E-BP1 in cancer

Ren Wang[a], Shridar Ganesan[b], and X. F. Steven Zheng[b]

[a]State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University Cancer Center, Guangzhou, China; [b]Rutgers Cancer Institute of New Jersey, Rutgers, the State University of New Jersey, New Brunswick, NJ, USA

ARTICLE HISTORY Received 14 March 2016; Revised 15 March 2016; Accepted 16 March 2016

KEYWORDS 4E-BP1; cancer; kinase; mTOR; translation

mTOR is a master regulator of cell growth and metabolism in eukaryotes, which is frequently activated during tumorigenesis and sustains uncontrolled growth and proliferation.[1] 4E-BP1 is a key substrate of mTOR and a repressor of protein synthesis. As such, 4E-BP1 is generally thought to negatively regulate growth and thus act as a tumor suppressor. Indeed, the ability of mTORC1 to inhibit 4E-BP1 has been correlated with the efficacy of mTOR-targeted therapies. Paradoxically, 4E-BP1 is frequently overexpressed in human cancers, suggesting that 4E-BP1 also has the capacity to promote tumor progression. In a recent review, Qin and colleagues provided a comprehensive analysis of some surprising non-canonical functions of 4E-BP1 in human cancer.[2]

mTOR is an evolutionarily conserved kinase that forms 2 distinct protein complexes, mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2), regulating growth and survival, respectively. mTORC1 is activated by growth factors and nutrients, especially amino acids. A major function of mTORC1 is to promote protein synthesis, partly through cap-dependent regulation of mRNA translation.[3] The rate of mRNA translation in eukaryotes is controlled at the initiation step through elongation initiation factor 4E (eIF4E) that directs the binding of ribosomes to the 5′-cap of mRNA.[3] 4E-binding protein 1 (4E-BP1) is a repressor of translation that prevents eIF4E from assembly into the pre-initiation eIF4F complex. Upon activation, mTORC1 kinase directly phosphorylates 4E-BP1. Hyperphosphorylated 4E-BP1 dissociates from eIF4E, leading to the formation of the pre-initiation eIF4F complex and initiation of protein synthesis.

As a major driver of oncogenesis, mTOR has long been recognized as a cancer therapeutic target.[4] The analogs of the nature product rapamycin, everolimus and temsirolimus, are allosteric mTORC1 inhibitors and FDA-approved anticancer drugs for treating advanced breast and renal cancers. A large number of mTOR kinase inhibitors have also been developed that are currently in human clinical trials. As expected for targeted therapy, resistance is frequently seen with mTOR inhibitors. One of the main mechanisms is mTOR-independent 4E-BP1 phosphorylation.[5] In drug-resistant colorectal cancer cells, mTOR inhibitors only transiently block 4E-BP1 phosphorylation, and 4E-BP1 becomes re-phosphorylated even when mTOR inhibition has persisted. This observation suggests that an alternative 4E-BP1 kinase(s) is activated in response to mTOR inhibition, which causes translational de-repression from 4E-BP1 in an mTOR-independent manner. Several protein kinases have been implicated in phosphorylation of 4E-BP1 in various contexts, including GSK-3, the p38 MAP kinase and its downstream kinase MSK1, ERK, PIM kinases, ATM and Cdc2/CDK1. However, none of these kinases thus far has been definitively shown to be responsible for resistance to mTOR kinase inhibitors.

Although the canonical function of 4E-BP1 is considered a growth suppressor, paradoxically, 4E-BP1 has been found widely overexpressed in human cancer. In some cases, 4E-BP1 overexpression has been correlated with poor prognosis. 4E-BP1 is seen overexpressed in malignancies of breast, gastrointestinal, head and neck, and prostate origins. A number of possible mechanisms have been described for 4E-BP1 overexpression. Gene amplification may drive overexpression as 4E-BP1 is present within the 8p12 amplicon, a common region of gene amplification found in multiple cancer including breast cancer, where it is associated with poor prognosis.[6] 4E-BP1 overexpression may itself promote a hypoxia-induced switch from cap-dependent to cap-independent mRNA translation, which favors translation of mRNAs involved in tumor angiogenesis and survival under hypoxic conditions.[7] Despite many years of intensive studies of cellular functions, the overall role of 4E-BP1 in human cancer remains not fully understood. Further research, especially those using physiologically relevant tumor models, is needed to untangle the complex relationship between the tumor suppressive and oncogenic functions of 4E-BP1.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

References

[1] Tsang C, et al. Drug Discov Today 2007; 12:112-24; PMID:17275731; http://dx.doi.org/10.1016/j.drudis.2006.12.008.

CONTACT X. F. Steven Zheng zhengst@cinj.rutgers.edu Rutgers Cancer Institute of New Jersey, Rutgers, the State University of New Jersey, 195 Little Albany Street, New Brunswick, NJ 08903, USA

News and Views to: Qin X, et al. 4E-BP1, a multifactor regulated multifunctional protein. Cell Cycle. 2016; 15: 781-6; PMID: 26901143; http://dx.doi.org/10.1080/15384101.2016.1151581

[2] Qin X, et al. Cell Cycle 2016; 15: 781-6; PMID:26901143; http://dx.doi.org/10.1080/15384101.2016.1151581
[3] Ma XM, Blenis J. Nat Rev Mol Cell Biol 2009; 10:307-18; PMID:19339977; http://dx.doi.org/10.1038/nrm2672.
[4] Zhang Y, et al. Drug Discov Today 2011; 16:325-31; PMID:21333749; http://dx.doi.org/10.1016/j.drudis.2011.02.008.
[5] Zhang Y, Zheng X. Cell Cycle 2012; 11:594-603; PMID:22262166; http://dx.doi.org/10.4161/cc.11.3.19096.
[6] Bilal E, et al. PloS one 2012; 7:e38575; PMID:22719901; http://dx.doi.org/10.1371/journal.pone.0038575.
[7] Braunstein S, et al. Mol Cell 2007; 28:501-12; PMID:17996713; http://dx.doi.org/10.1016/j.molcel.2007.10.019.