

The AMPK-MNK1 signaling axis

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Valorization

In addition to the scientific relevance of this thesis, the presented work uncovered a new research area that could offer leads for future therapeutic strategy development and thus carries promising societal relevance.

Social relevance of the study objectives

Modern worldwide economic development has induced dramatic changes in lifestyle and the Metabolic syndrome has become one of the biggest threats for healthy living. The Metabolic syndrome is a cluster of the most prominent heart disease risk factors, including diabetes and obesity, which has a prevalence of 20-25% in adults worldwide. Diabetes itself has become a top cause of death in developed countries. Logically, the burden on healthcare systems is rising dramatically and the cost of treatment is enormous [1].

Due to its crucial role in energy-balance, AMPK is a highly valuable pharmacological target in the treatment of metabolic disorders. However, at present only a subset of AMPK functions and substrates have been elucidated. By revealing more downstream targets of AMPK, a more complete functional map could be obtained, which could potentially offer various possibilities for prevention of disease development, or specific treatment options for certain risk factors. Regarding MNK1 function, most recently a novel role of MNKs has been reported in mediating HFD-induced insulin resistance [2], in light of the discoveries described in this thesis, this could represent a new hidden therapeutic connection with AMPK.

Similarly, as one of the other leading causes of morbidity and mortality worldwide, cancers in 2012 reached approximately 14 million new cases and 8.2 million deaths [3]. The survival rate of diverse cancers are known to vary among types and stages and they range between disease-free survival to mortality within five years after diagnose. More strikingly, although several treatment methods have been developed for cancer therapy, the long-term side effects of these methods are almost as destructive to a patients' health as the disease itself, both physically and mentally. As a result, research in the field of cancer therapy, focusses on identification of underlying molecular mechanisms in individual cases and defining personalized approaches. Thus far, the exact role of AMPK in cancer remains unclear due to its two-faced involvement: several tumor types have been observed with loss of AMPK activity, while AMPK activation may be advantageous for other tumors cells to adapt to metabolic stress [4]. In contrast, high eIF4E expression has been found in many tumor cell lines and even in solid tumors, including cancers of breast, lung, prostate and colon [5]. As the sole-known upstream kinase of eIF4E, MNKs have therefore been treated as cancer therapy targets and have also been associated to

drug resistance. In this thesis we aimed to determine a potential connection between AMPK and MNK1 to understanding their functional relationship in cell growth control and to advance insight in their potential application in cancer treatment.

Novelty of the concept

Current knowledge of MNK1 as a therapeutic target in cancer is limited to its regulation on eIF4E phosphorylation in response to both growth factors and stress via ERK/P38. Yet, relatively little is known concerning the exact mechanisms of its activation and functional regulation. In this thesis, we further developed a probable MNK1 activation model based on earlier reported structural models. We described its localization to both cytoplasm and nuclei, potentially revealing a role on both translational and transcriptional processes. The novel link of MNK1 to AMPK may be interpreted as evidence for its potential involvement in metabolic disorders. The results thus far showed a non-linear correlation between them eIF4E activity and cellular translation level, implying a more delicate/selective control of eIF4E in protein translation. From the perspective of AMPK, the novel connection to regulation of MNK1 activity has extended its role in protein translation, which previously comprised the mTOR signaling pathway. These observations may be at the basis of AMPKs dual role in cell proliferation, growth control and cancer.

Future directions & potential applications

The extended knowledge of MNK1 in this thesis could be applied to related studies of both MNK1 structure analysis and MNK1-dependent signaling pathways. Several studies have indicated that location matters: subcellular compartmentalization of particular proteins restricts molecular interactions and dictates function and regulation. This concept applies to AMPK as well as MNK1, as both appear to “shuttle” between the cytoplasm and the nucleus. Future studies should be aimed at further elucidation of the biological relevance of AMPK and MNKs subcellular localization.

Beyond the directions above, this study has proven the protein microarray screening as an efficient and accurate technology and this method shows high potential for a broad application of substrate-screening for other protein kinases. In addition, the novel antibody we have generated in this study, has been proven to be effective in detection of a specific activity state of MNK1, and is expected to improve our knowledge on the exact conditions, mechanisms and relevance of MNK1a regulation. Given the observation that many more post-translationally modified, potentially regulatory amino acid residues await identification, both in AMPK and MNK, this holds promise for research as well as marketing avenues.

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