

Cancer Physiology Project

Introduction

Cancer cells in solid tumors frequently encounter a shortage of nutrients. Tumor microvasculature is structurally and functionally abnormal and not sufficient to supply the blood flow needed by proliferating cancer cells. Furthermore, some aggressive malignant tumors, such as pancreatic cancers, are hypovascular. Many cancer cells have acquired “austerity,” a tolerance to nutrient starvation, to survive in this unfavorable microenvironment. Since chronic nutrient starvation seldom occurs in normal tissue, austerity will be a novel and selective target for cancer therapy.

Novel Anticancer Agents Based on an Anti-austerity Strategy

Extracts of traditional medicine were applied to the *in vitro* screening system for exploring novel agents which inhibit the austerity of cancer cells. Dichloromethane-soluble extracts of *Arctium lappa* exhibited preferential cytotoxicity against nutrient-deprived cells *in vitro*. Arctigenin (C₂₁H₂₄O₆) was isolated from the extract as the primary compound responsible for this toxicity. Arctigenin also exerted antitumor activity against human pancreatic cancer cell line PANC-1 *in vivo* and suppressed AKT phosphorylation during glucose deprivation as well as previously identified anti-austerity agents such as kigamicin D and pyrvinium pamoate (92). Another compound, methyl abieta-8,11,13-trien-18-oate was isolated from “Pini Resina” and showed anti-austeric activity *in vitro* (93). The *in vivo* antitumor activity of kigamicin D was examined in the mouse model (94).

Development of an AMPK Activity Assay Method

5'-AMP-activated protein kinase (AMPK) has been found to regulate austerity. Conventional

AMPK activity assay is not efficient for crude AMPK preparations. *In vitro* kinase activity assay using GST-fused SAMS peptide as an AMPK substrate was established. This system is a convenient and rapid method of measuring AMPK activity (95).

Involvement of ARK5 in Tumor Progression

ARK5 is a recently identified AMPK-related serine/threonine protein kinase. It plays a pivotal role in hypoxia-induced tolerance to glucose starvation of hepatoma cells. ARK5 also regulates cell survival and migration activity. Increased ARK5 expression was also observed in clinical samples of colorectal cancer and multiple myeloma and was associated with the aggressive phenotype of these tumors. These findings imply the relevance of ARK5 to austerity and tumor progression (96). ARK5 gene is a target of large-MAF transcription factors. T-cell specific *c-maf* transgenic mice developed T-cell lymphoma. ARK5 expression was upregulated in c-Maf transgenic lymphoma cells. Correlated overexpression of c-Maf and ARK5 was also observed in human angioimmunoblastic T-cell lymphoma samples (97). Phosphorylation of threonine residue in the kinase domain is required for the full activation of ARK5. An oncogenic serine/threonine protein kinase, NDR2, was identified as an authentic upstream kinase of ARK5. NDR2 was activated on stimulation with IGF-1 and directly phosphorylated ARK5. NDR2 mediated IGF-1-induced cell survival and invasion signals via ARK5 (98). These findings strengthen the possible involvement of ARK5 in tumor progression.

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