Cancer Chemoprevention Locks onto a New Polyamine Metabolic Target

Perspective on Plym Forshell et al., p. 140

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Abstract

Ornithine decarboxylase has a relatively long history as a target for cancer chemoprevention and chemotherapy. Plym Forshell et al. report new evidence (beginning on p. 140 in this issue of the journal) indicating that spermidine synthase, a fellow enzyme of ornithine decarboxylase in polyamine metabolism, is transactivated in part by the MYC gene and is a potential target for chemoprevention of B-cell lymphomas. Cancer Prev Res; 3(2): 125–7. ©2010 AACR.

Introduction

Increased polyamine metabolism has long been associated with normal growth and development and with neoplasia (reviewed in ref. 1). Meyskens et al. (2) reported in 2008 that a combination of drugs including one targeting ornithine decarboxylase (ODC), which is the first enzyme in polyamine synthesis and is induced by the MYC oncogene, dramatically reduced the incidence of metachronous colorectal adenomas in patients with prior colon polyps. In this issue of the journal, Plym Forshell and colleagues (3) report that the MYC oncogene induces spermidine synthase (SRM), another enzyme in polyamine metabolism, in a murine model of B-cell lymphoma; they showed that inhibition of SRM increases tumor-free survival of these mice. This finding provides new evidence that SRM is a second MYC-inducible gene (after ODC) in polyamine metabolism and thus is a target for cancer chemoprevention.

The selective ODC inhibitor difluoromethylornithine (DFMO) was synthesized in the 1970s and was evaluated as a possible cancer therapy, but it had limited efficacy in early-phase clinical therapeutic trials (4). Inhibitors of other polyamine metabolic enzymes were developed. SAM486A, which inhibits S-adenosylmethionine decarboxylase, produced minimal efficacy in cancer therapeutic trials, stalling its further development (5). Extensive preclinical evidence supporting DFMO as a potential chemopreventive agent for many types of cancer began to be reported in the 1980s (6). Epidemiologic results from two independent groups supported the preclinical studies, as a genetic variant in the ODC promoter was associated with risk of colorectal adenoma formation in patients with an average risk of colon cancer (7, 8). The positive preclinical and molecular epidemiologic data on DFMO led to its development as a potential cancer chemopreventive agent during the 1990s (9). In a phase IIb/III clinical trial of a combination of single daily oral doses of DFMO and the nonsteroidal anti-inflammatory drug (NSAID) sulindac (rationale reviewed in ref. 10) versus placebo for 3 years, the combination was associated with a dramatic reduction in metachronous colorectal adenomas (2). Treatment-associated toxicities were minimal (11, 12). Additional clinical evidence for the efficacy of DFMO in reducing certain cancer risk factors includes results of topical DFMO in reducing the number of premalignant skin actinic keratosis lesions (13) and of oral DFMO in reducing the incidence of basal cell carcinoma in a recent phase III trial (14). Daily oral doses of DFMO have been associated with reduced (versus placebo) prostate levels of polyamines, lesser increases in prostate volume, and slower doubling times of prostate-specific antigen in men with a family history of prostate cancer (15).

The new work by Plym Forshell and colleagues (3) is significant for its identification and validation of the new target SRM, a second MYC-regulated gene product in the polyamine pathway, for cancer chemoprevention. The further significance of SRM is provided by its validation as a chemoprevention target in a model of B-cell lymphomas, which expands the tissue types in which polyamine metabolism–related carcinogenesis seems to occur. MYC has been implicated in several cancers (16). MYC functions by transactivating many target genes, including several genes involved in polyamine metabolism and function. MYC targets in the polyamine biosynthetic pathway include ODC (17), AMD1 (18), and SRM (3), as depicted in Fig. 1. These three genes work in concert to produce the polyamine spermidine. MYC also regulates the expression of genes affecting the polyamine uptake from extracellular sources. Polyamine transport is negatively regulated by a caveolin-1 (CAV-1)–dependent endocytic
mechanism (19). CAV-1 is in turn negatively regulated by MYC acting on noncanonical E-box response elements in the CAV-1 promoter (20). Therefore, MYC expression would act to increase polyamine transport and tissue polyamine levels by repressing CAV-1 expression.

In addition to transactivating these genes, MYC is capable of transactivating the eIF5A2 gene in some cells (21). The eIF5A2 gene product, such as the related eIF5A1 protein, undergoes a unique posttranslational modification, requiring spermidine as a substrate and resulting in the conversion of a lysine residue to the novel amino acid hypusine (22).

The hypusine modification in eIF5A1 is required for the protein’s activity in stimulating methionyl-puromycin formation, a model of first peptide bond formation during protein synthesis (23). Stitz and coworkers (24) recently reported a structural mechanism for the role of EF-P, a bacterial homologue of eIF5A, in facilitating first peptide bond formation. These findings may provide some clues to the mechanisms by which polyamines facilitate, and inhibitors of ODC and SRM may prevent, carcinogenesis. Retroviral transduction of an Elf5a2, but not an Elf5a1, cDNA into p53−/−;Myc hepatocytes caused tumor formation when the cells were injected s.c. into nude mice (25). As suggested in Fig. 1, polyamines and the hypusine modification in eIF5A may mediate the oncogenic potential of MYC in specific cell types and tissues, and may explain the efficacy of DFMO in reducing cancer risk factors in clinical trials, as discussed earlier.

Some polyamine metabolic genes implicated in carcinogenesis are not known to be targets of MYC. One example, the product of spermidine/spermine N1-acetyltransferase (SAT1), is overexpressed, along with ODC, in neoplastic compared with normal human prostate tissue (26). Overexpression of SAT1 suppresses prostate tumor growth in the TRAMP model of prostate carcinogenesis (27). Activation of SAT1 is a potential mechanism of the anticarcinogenic and chemopreventive effects of NSAIDs in colon cancer models (28–30).

A final significant aspect of the present Plym Forshell et al. (3) contribution is the potential identification of a rational target for new strategies of combination cancer chemoprevention, a concept first proposed 30 years ago by Michael Sporn for increasing activity and lowering individual doses, and thus lowering toxicity (31). The rationale for the combination of DFMO plus sulindac for preventing metachronous colorectal adenomas (discussed earlier) included results from both human cell line and translational studies, and mouse models showing that sulindac activated polyamine catabolism and export, in addition to its effects on cyclooxygenases in arachidonic acid metabolism (32). Therefore, sulindac and other NSAIDs work in concert with DFMO to suppress target tissue polyamine contents. SRM inhibitor combinations that may also prove to be effective include their combination with NSAIDs (an alternate to DFMO plus sulindac for targeting polyamine synthesis and inflammation), DFMO (two agents targeting different aspects of polyamine synthesis), and/or polyamine transport inhibitors (33).

Future advances in cancer chemoprevention will require steps that increase benefit-to-risk ratios (34). DFMO and NSAIDs have proved effectiveness in treating certain cancer
risk factors but also have well-established, albeit frequently severe, toxicities (11, 35). The combination of DFMO plus sulindac allowed substantially lower, less-toxic effective doses of each agent. SRM inhibitors may prove to be an alternative to DFMO in future combination strategies for treating cancer risk factors.

References


Disclosure of Potential Conflicts of Interest

E.W. Gerner has an ownership interest in Cancer Prevention Pharmaceuticals, Tucson, Arizona.

Received 10/29/09; revised 11/24/09; accepted 11/27/09; published Cancer Prev Res OnlineFirst 1/26/10.
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doi:10.1158/1940-6207.CAPR-09-0252

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