NOVEL LIPIDS AND CANCER

Isoprenoids and Other Phytochemicals

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1. INTRODUCTION

The focus of studies of diet/cancer interrelationships is shifting from the roles nutrients play to the chemopreventive actions of plant-derived, non-nutrient dietary constituents (indoles, coumarins, phthalides, organosulfur compounds, phytoestrogens, isothiocyanates, bioflavonoids and protease inhibitors). Our interest in this aspect of diet/health relationships has roots in findings that products of plant mevalonate pathways both suppress hepatic mevalonate synthesis with a concomitant lowering of serum LDL cholesterol level and suppress the growth of chemically-initiated and transplanted tumors.¹-⁴ Some of the more effective end products derived from the sequential mevalonate pathway intermediates, geranyl pyrophosphate, farnesyl pyrophosphate and geranylgeranyl pyrophosphate, are listed on Figure 1.¹, ² The pathway provides essential dietary components, specifically phyloquinone, β-carotene and α-tocopherol. The monoterpenes and sesquiterpenes have no nutritional impact. Never the less each of the products listed on Figure 1 has been shown to have an impact on HMG CoA reductase activity, blood cholesterol level and tumor cell proliferation.¹-⁴

The isoprenoids emphasized in this presentation, β-ionone and γ-tocotrienol, are related to β-carotene and α-tocopherol, the “antioxidant vitamins” linked by epidemiological data⁵, but not by randomized experimental trials⁶, with a reduced incidence of cancer. β-Ionone has no antioxidant activity and that of γ-tocotrienol is marginal; both are potent suppressors of hepatic mevalonate synthesis. We postulate that the isoprenoid-mediated suppression of mevalonate synthesis diminishes the pool of mevalonate pathway intermediates which are required cholesterol synthesis and for the post translational modification of proteins essential for cell survival (Figure 2). We further postulate that the isoprenoid-mediated suppression of tumor growth traces to the restrictions this action imposes on the post translational modification of nuclear lamins and ras oncoproteins (Figure 2). As shown on Figure 2 the mevalonate pathway offers targets for controlling cholesterol synthesis and tumor growth with lovastatin and mevinolin⁷, sodium phenylacetate⁶ and fluoromevalonate⁸.
Figure 1. Intermediate and end products of mevalonate metabolism in plant tissues. HMG CoA reductase is the rate-limiting activity for the synthesis of mevalonic acid, the rate-limiting substrate for the synthesis of the isoprenoid products shown to have tumor-suppressive actions.

Figure 2. Intermediate and end products of mevalonate metabolism in animal tissues. HMG CoA reductase is the rate-limiting activity for the synthesis of mevalonic acid, the rate-limiting substrate for the synthesis of the cholesterol. Competitive inhibitors of HMG CoA reductase activity (Lovastatin and related products) are widely prescribed for the control of hypercholesterolemia. HMG CoA reductase activity in tumor cells is elevated and resistant to sterol feedback regulation.