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The “One-Two Punch” of Isoprenoids to Inflammation

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A large body of evidence from recent studies has shown that tocotrienols, the vitamin E molecules with an unsaturated farnesyl side chain, have potential in the prevention and/or treatment of cancer, metabolic syndrome, obesity, diabetes, osteoporosis, and neurodegeneration [1]. These activities of tocotrienols may converge on the emerging finding that tocotrienols suppress the activation of nuclear factor kappa B (NFκB), a major mediator in chronic inflammation that is gaining recognition as one of the main mechanisms underlying these chronic diseases. Tocotrienol-mediated inhibition of NFκB DNA binding activity or suppression of tumor necrosis factor α- and lipopolysaccharide-induced NFκB expression has been demonstrated in human breast cancer cells [2,3], colon carcinoma cells [4], malignant melanoma cells [5], pancreatic cancer cells [6], gastric cancer cells [7], metastatic oral cancer cells [8], adipocytes [9], and macrophages [10]. Moreover, the *in vitro* NFκB-suppressive activity of tocotrienols was borne out in gastric cancer [7] and pancreatic cancer [11] in nude mice. Readers are referred to recent reviews [12-14] for more details on the anti-inflammatory activity of tocotrienols.

A closer examination of the NFκB-suppressive activity of tocotrienols revealed a more fundamental biological activity of tocotrienols; NFκB suppression may be a secondary effect of tocotrienol-mediated down-regulation of another biochemical pathway that is ubiquitous in virtually all eukaryotic cells: the mevalonate pathway [15]. The mevalonate pathway operating in sterologenic tissues provides – in addition to cholesterol that is an essential component of cell membrane and a precursor to vitamin D, bile acids and steroid hormones-essential intermediates including farnesyl- and geranylgeranyl- pyrophosphates for the post-translational prenylation of growth-related proteins such as Ras and nuclear lamins and N-linked glycosylation of insulin-like growth factor receptor I. Most importantly, prenylated Ras activates NFκB [16].

The rate-limiting enzyme in the mevalonate pathway, 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase, is under a multivalent regulation consisting of sterol-mediated transcriptional feedback inhibition and a non-sterol-mediated post-transcriptional down-regulation. Tocotrienols suppress HMG CoA reductase at both transcriptional and post-transcriptional levels [17] and consequently, deplete the pool of prenyl pyrophosphates required for the prenylation of Ras and inactivate NFκB. Ahn et al. showed that tocotrienol-mediated ablation of NFκB activity was reversed by supplemental mevalonate, the product of the reaction catalyzed by HMG CoA reductase [15], establishing mevalonate deprivation as the primary cause for NFκB inactivation.

Tocotrienols may represent a broad class of isoprenoids encompassing approximately 23,000 mevalonate-derived end-products of plant secondary metabolism. Isoprenoids can be classified based on the number of isoprene units they contain, e.g. monoterpene (2x), sesquiterpene (3x), diterpene (4x), triterpene (6x) and polyterpene (Nx) [18]. In addition to these “pure” isoprenoids, the “mixed” isoprenoids including the tocotrienols have non-mevalonate-derived moieties. Assorted isoprenoids have a wide spectrum of functions in the plant kingdom, ranging from growth regulation to insect attraction, pollination assistance, and pest resistance. Fruits, vegetables and grains are the main sources of dietary isoprenoids.

The HMG CoA reductase-suppressive activity is extensively

observed among isoprenoids [19]. It is therefore no coincidence that a number of isoprenoids under investigation also suppress NFκB activity. The monoterpene limonene inhibited NFκB activation in human HL60 clone 15 leukemia cells [20] while an oxidative product of limonene, perillyl alcohol, suppressed NFκB in B-lymphoma cells [21]. A third monoterpene, geraniol, suppressed 12-O-tetradecanoyl phorbol-13-acetate (TPA)-induced inflammatory responses and up-regulation of NFκB and COX-2 in mice [22]. A sesquiterpene β-ionone inhibited tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-induced NFκB activation in human HepB3 and HepG2 hepatocellular carcinoma cells [23]. Various sesquiterpene lactones blocked NFκB activity [24]. Diterpene coronarin D suppressed NFκB activation in human KBM-5 chronic myeloid leukemia and A293 embryonic kidney carcinoma cells [25]. Garcinol, a polyisoprenylated benzophenone, inhibited the activation of NFκB in human BxPC-3 and Panc-1 pancreatic cancer cells [26] and squamous cell carcinoma of the head and neck [27]. Lastly, a triterpene lupeol suppressed TPA-induced activation of NFκB in CD-1 mice [28].

More support for the mevalonate-inflammation connection is drawn from studies with the statins, competitive inhibitors of HMG CoA reductase, and protein prenyl transferase inhibitors showing their parallel impacts on NFκB. Simvastatin inhibited NFκB activation in human COLO 205 colon cancer cells [29], squamous cell carcinoma SCC4 cells and KBM-5 cells [30]. Statins also suppressed the tumor necrosis factor α- [31] and receptor activator of NFκB ligand (RANKL) - [32] induced activation of NFκB in RAW 264.7 macrophages. C-reactive protein-induced NFκB activation was inhibited by simvastatin in human umbilical vein endothelial cells; reminiscent of the findings by Ahn et al. with tocotrienols [15], mevalonate attenuated the simvastatin effect on NFκB [33]. Consequent to Ras inactivation [34], farnesyl transferase inhibitors FTI-276 and SCH 66336 suppressed NFκB activation in rheumatoid arthritis synovial fibroblasts [35], human Jurkat T-cell lymphoma cells, H1299 lung adenocarcinoma cells, MCF-7 breast adenocarcinoma cells, and A293 embryonic kidney cells [34].

By depleting mevalonate and consequently suppressing NFκB activity, isoprenoids and most prominently tocotrienols may deliver a “one-two punch” to inflammation. The omnipresence of the mevalonate pathway and the critical role of inflammation in chronic disorders suggest that dietary isoprenoids warrant further investigation for their potential roles in the prevention and managing of chronic diseases.

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