SESSION 10

The Future of Cancer (Chemo)Prevention

S33. Angiogenesis & Cancer Prevention: A Vision

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Angiogenesis is necessary for solid tumor growth and dissemination, in addition to angiogenesis, it has become increasingly clear that inflammation is a key component and/or inflammation tumor insurgence that can promote tumor angiogenesis. We note that angiogenesis are a common and key target of most chemopreventive molecules, where they most likely suppress the angiogenic switch in pre-malignant tumors, a concept we termed "Angioprevention". We have shown that various molecules, such as flavonoids, antioxidants and retinoids, act in the tumor micro-environment inhibiting the recruitment and/or activation of endothelial cells and phagocytes of the innate immunity. N-acetyl-cysteine, the green tea flavonoid epigallocatechin-3-gallate (EGCG), and Alpha lipoic acid (ALA) all prevent angiogenesis in the Matrigel sponge angiogenic assay in vivo and inhibit the growth of the highly angiogenic Kaposi's sarcoma tumor cells (KS-Imm) in nude mice. The synthetic retinoid 4-hydroxyfenretinide (4HPR) also showed anti-angiogenic effects. We analyzed the regulation of gene expression they exert in primary human umbilical endothelial cells (HUVEC) in culture with functional genomics. Expression profiles obtained through Affymetrix GeneChip arrays identified overlapping sets of genes regulated by the anti-oxidants. In contrast, the ROS-producing 4HPR instead induced members of the TGFβ-ligand superfamily, which, at least in part, explains its anti-angiogenic activity. NAC and the flavonoids all suppressed the IkB/NF-kB signalling pathway even in the presence of NF-kB stimulation by TNFα, and showed reduced expression of many NF-kB target genes. A selective apoptotic effect on transformed cells, but not on endothelial cells, of the anti-oxidants may be related to the reduced expression of the NF-kB dependent survival factors Bcl2 and Birc5/surviving, that are selectively over-expressed in transformed cells, by these factors. The repression of the NF-kB pathway suggests anti-inflammatory effects for the anti-oxidant compounds that may also represent an indirect role in angiogenesis inhibition. The green tea flavonoid EGCG does target inflammatory cells, mostly neutrophils, and inhibits inflammation-associated angiogenesis. The other angiopreventive molecules are turning out to be effective modulators of phagocyte recruitment and activation, further linking inflammation and vascularization to tumor onset and progression and providing a key target for cancer prevention.