The goals of this symposium were to provide an update on the pathways and possible mechanisms by which vitamin A, its principal metabolite retinoic acid (RA)\(^3\) and related synthetic retinoids may prevent carcinogenesis in cell models and intact organisms. The idea that vitamin A is important for the prevention of cancer is far from new. Studies in the early 1900s showed that vitamin A deficiency is associated with a propensity for tumor development. In the late 1940s all-trans-RA was characterized and subsequently shown to be responsible for most of the biological activities ascribed to vitamin A, except for those in the visual cycle. Although it was suspected that RA functions as a hormone, the elucidation of its specific hormonal mechanism of action awaited the discovery of nuclear retinoid receptors in the late 1980s. In the meantime research relating vitamin A to cancer was further stimulated by the demonstration that RA and certain synthetic analogues can induce the differentiation of undifferentiated embryonal stem cells or poorly differentiated cells and inhibit the proliferation of activated or transformed cells. The anticancer activity of vitamin A, RA and its now-numerous analogues has been demonstrated in a variety of animal models of spontaneous and induced cancers. The successful clinical application of retinoids in dermatology raised hopes further that synthetic retinoids might be powerful tools in the prevention and treatment of human cancers. Retinoid research expanded and broadened greatly after the discovery of the nuclear retinoid receptors, retinoic acid receptor (RAR) and retinoid X receptor (RXR), two gene families within the gene superfamily of steroid hormone receptors (reviewed in 1). With this new understanding it became possible to elucidate a powerful mechanism of action, first for all-trans-RA, a high affinity ligand of the RXRs (RXR\(\alpha\), \(\beta\) and \(\gamma\)), and subsequently for its isomer, 9-cis-RA, a specific ligand of the RRRs (RXX\(\alpha\), \(\beta\) and \(\gamma\)). The importance of understanding retinoid biology was further underscored by the demonstration that the RXR interacted as the necessary dimeric partner not only with RARs but with several other families of the steroid receptor superfamily, including the vitamin D receptor and some nuclear proteins originally classified as orphan receptors and now known to be activated by, for example, fatty acids and prostanoids (peroxisome proliferator-activated receptors), sterols and bile acids (liver X receptor and farnesol X receptor) and xenobiotics (steroid and xenobiotic-activated receptors) (reviewed in 2).

It is now understood that retinoids are involved in nearly all vertebrate biological systems. One current research thrust is to better understand the retinoid-regulated genes that directly control the differentiation of human stem cells. Such genes may suppress tumorigenesis or even reverse the malignant phenotype. In this symposium, Spinella et al. (3) review studies using pluripotent, unspecialized human embryonal carcinoma cells to identify and characterize the target genes responsible for retinoid-induced cell differentiation. The use of microarray techniques has revealed several rapidly induced targets of RA, including receptor-interacting protein 140.

Soprano and Soprano (4) discuss another interesting interaction, that between some retinoids and the aryl hydrocarbon receptor (AhR). The AhR is well known to be activated by certain carcinogenic xenobiotics and to be important in inducing the cytochrome P450-mediated activation of certain carcinogens. Their studies demonstrate that some retinoids, in addition to modulating the RAR/RXR pathway, are capable at pharmacologic concentrations of binding to the AhR and activating its pathway.

Many genes are not direct transcriptional targets of RA but nevertheless are induced or repressed by retinoid treatment. In this symposium, Niles (5) reviews studies on the regulation of gene expression in the B16 murine melanoma cell model. Gene array studies revealed a small number of genes that reproducibly responded to RA, including the immediate-early (directly activated) gene T-box binding protein-2 (Tbx-2). Protein kinase C, which was not a direct target of RA, still was strongly induced and appeared to be required for the biological effects of RA in B16 melanoma cells.

The final two papers in this symposium address aspects of retinoid status in vivo that may be related to the development or the prevention of cancer. A current hypothesis is that the depletion of tissue retinoids creates an environment susceptible to carcinogenesis. A corollary is that a dietary inadequacy of vitamin A may foster tumor initiation or promotion and, conversely, that exogenous vitamin A or RA may be preventive. The liver, the body’s major vitamin A storage organ...
and a significant site of retinoid metabolism, is also susceptible to diet-related carcinogenesis. The research reviewed by Wang (6) focuses on research on alcohol-induced hepatic carcinogenesis in a rat model. Alcohol is well known to induce a depletion of liver retinoids and is associated with an increased incidence of several human cancers. Although ethanol deregulated apoptosis and induced the activator protein-1 pathway and cellular proliferation in rat liver, the restoration of hepatic retinoid homeostasis by treatment with RA or inhibition of RA catabolism suppressed these alcohol-induced effects. Finally, Ross (7) reviews studies on the regulation of retinoid metabolism by dietary vitamin A and exogenous RA. At least two genes in the retinoid biosynthetic pathway are highly sensitive to vitamin A status in vivo, as well as to exogenous RA. It is proposed that RA serves as a positive regulator of retinol esterification in liver and lung, as well as an inducer of its own cytochrome P450-mediated catabolism when RA is in excess. These studies help to identify physiological targets that may function to control the availability of bioactive retinoids.

**LITERATURE CITED**