Chemoprevention of liver carcinogenesis with retinoids: Basic and clinical aspects.

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The strategy to prevent liver carcinogenesis consists of: (i) antiviral modalities such as vaccination, lamivudin, and interferon; (ii) anti-inflammatory modality; and (iii) chemoprevention using such compounds as retinoid analog and vitamin K. Cancer chemoprevention is defined as an approach where natural or synthetic chemical compound works to arrest or reverse premalignant cells by using physiological pathways. As a consequence, such a clone of premalignant cells is eradicated (clonal deletion) by differentiation induction or apoptosis, and thus the process toward the development of clinically detectable cancer is disrupted. A particularly effective candidate target of chemoprevention in liver diseases is an advanced stage of chronic hepatitis, that is supposed to contain transformed hepatocyte clone(s); that is, primary prevention from liver cirrhosis and prevention of recurrent and second primary hepatocellular carcinoma following the treatment of the initial cancer. Retinoid is a collective term of vitamin A analog that binds to nuclear retinoid receptors; retinoic acid receptors (RAR) and retinoid X receptors (RXR). After ligand coupling, these receptors form homo- or heterodimers, bind to the response element (RARE or RXRE) upstream of the target gene, and regulate the gene expression as a transcriptional factor. Biological phenotypes of such transcriptional regulation by retinoid include cellular differentiation, tissue morphogenesis, and programmed cell death (apoptosis). Due to these functions, retinoid analogs are clinically tried to prevent/treat carcinoma in a wide variety of organs including head and neck cancer, uterine cervical cancer, certain leukemia and liver cancer. In this article, clinical trials of retinoid analog to inhibit second primary hepatoma, supposed molecular mechanism of
the action of the compound, and aberrant metabolism of RXR and its role in liver carcinogenesis are briefly reviewed.

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