



Retinoids and Their Receptors in Cancer

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BIOGRAPHY

Xiao-kun Zhang earned his Ph.D. in biochemistry from the University of Vermont in 1989. Dr. Zhang spent three years as a postdoctoral fellow at the Burnham Institute prior to his appointment to the faculty in 1992.

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Dr. Xiao-kun Zhang studies the chemopreventive and therapeutic effect of Vitamin A and its synthetic analogs in various cancers and diseases. Dr. Zhang found that a gene called RAR β that binds Vitamin A acts to prevent cancer cell growth. Unfortunately, RAR β is lost in many cancers, and Dr. Zhang has discovered new approaches to restore RAR β levels and activities in cancer cells by using a group of new agents that bind RXR, another vitamin A binding protein. One of these agents has been approved by the FDA for treating cancer patients. Recently, Dr. Zhang discovered a new paradigm for destroying cancer cells by using a protein called TR3. TR3 is often present at high levels in cancer cells to promote their growth in the nucleus. Dr. Zhang recently showed that he is able to move TR3 from the nucleus to another intracellular organelle called the mitochondria. Such a migration of TR3 from the nucleus to mitochondria effectively destroys cancer cells. Dr. Zhang is now exploring the possibility of using a class of specific agents for treating cancer by inducing the TR3 migration.

Our laboratory focuses on the retinoid receptors in cancer cells and the development of new retinoids with optimal anti-cancer activities. Retinoids are a group of natural and synthetic vitamin A analogs and are promising agents for the prevention and treatment of a variety of cancers and diseases. The major limitation to the application of retinoids is the retinoid resistance observed in cancer cells. Our goal is to understand how anticancer activities of retinoids are regulated and how cancer cells acquire resistance to retinoids with the aim of restoring retinoid sensitivity in cancer cells and developing more effective retinoids for cancer prevention and treatment.

The anti-cancer effects of retinoids are mainly mediated by their nuclear receptors, the retinoic acid (RA) receptors (RARs) and the retinoid X receptors (RXRs). During the last few years, we have devoted our effort to understand the mechanisms by which retinoids inhibit cancer cell growth. We found that retinoids can promote apoptosis in breast cancer and lung cancer cells and that induction of apoptosis and growth inhibition by retinoids is largely mediated by RAR β . Our results suggest that RAR β may function as a tumor suppressor gene in lung and breast carcinogenesis, and that loss of RAR β may contribute to the tumorigenicity and retinoid resistance of cancer cells.

New Retinoid Signaling in Cancer Cells.

We showed that the conventional retinoids, such as trans-RA, effectively induce RAR β expression and inhibit the growth of hormone-dependent but not hormone-independent breast cancer cells. Induction of RAR β in hormone-dependent breast cancer cells is mediated by RAR/RXR heterodimer that binds to the RA response element (β RARE) in the RAR β promoter. Recently, we have identified a new pathway to induce RAR β in hormone-independent breast cancer cells by using RXR-selective retinoids, such as 9-cis RA. This pathway is mediated by RXR/nur77 heterodimer that binds to the same β RARE. Thus, depending on levels of RAR, RXR and nur77, either a RAR or a RXR signaling pathway can induce RAR β expression and apoptosis in breast cancer cells (Figure 1). Such a retinoid signaling switch may play an important role in regulating cell growth in response to different stimuli, and it suggests that different retinoids can be used to inhibit the growth of different types of breast cancer.

New Apoptosis-inducing Retinoids.

6-[3-(1-adamantyl)-4-hydroxyphenyl]-2-naphthalene carboxylic acid (AHPN or CD437) was originally identified as a retinoic acid receptor γ (RAR γ)-selective retinoid. We investigated the role of AHPN/CD437 and its mechanism of action in human lung cancer cell lines. Our results demonstrated that AHPN/CD437 effectively inhibited lung cancer cell growth by inducing G0/G1 arrest and apoptosis, a process that is accompanied by rapid induction of cJun, nur77 and p21. In addition, we found that expression of p53 and Bcl-2 was differentially regulated by AHPN/CD437 in different lung cancer cell lines and may play a role in regulating AHPN/CD437-induced apoptotic process. Furthermore, overexpression of nur77 anti-sense RNA in A549 and H460 lung cancer cell lines largely inhibited AHPN/CD437-induced apoptosis. Thus, expression of nur77 plays a critical role in AHPN/CD437-induced apoptosis. Together, our study reveals a novel pathway for retinoid-induced apoptosis and suggests that AHPN/CD437 or analogs may have a better therapeutic efficacy against lung cancer.

Regulation of RAR β Expression and Retinoid Sensitivity by Orphan Receptor COUP-TF

How RAR β expression is regulated and how its expression is lost in cancer cells remain largely unknown and are subject to intensive studying. Expression of RAR β is highly induced by RA and requires RAR and RXR that bind to the β RARE present in its promoter. However, expression of RARs and RXRs is not sufficient to render RAR β expression responsive to RA. In searching for factors, other than RARs and RXRs, that are required for RAR β expression and responsible

for loss of retinoid sensitivity in cancer cells, we have identified that orphan receptor COUP-TF plays a key role in modulating RAR β expression and retinoid sensitivity in cancer cells. Expression of COUP-TF is positively correlated with RAR β induction and growth inhibition by RA in various cancer cell lines. Our stable transfection assays showed that expression of COUP-TF in COUP-TF-negative cancer cells enhanced induction of RAR β expression, growth inhibition and apoptosis by RA, while inhibition of COUP-TF by expression of COUP-TF anti-sense RNA in COUP-TF-positive cells repressed the ability of RA to induce RAR β expression, growth inhibition and apoptosis in the cells. In transient transfection assay, COUP-TF strongly induced transcriptional activity of the RAR β promoter in a RA- and RAR α -dependent manner. The effect of COUP-TF requires both a DR-8 element that binds strongly with COUP-TF and the β RARE in the RAR β promoter. Mutations that either abolished COUP-TF binding to the DR-8 element or RAR α binding to the β RARE impaired RA- and RAR α - dependent transactivation function of COUP-TF. By GST-pull-down assay, we observed that COUP-TF, through its interaction with RAR α with its co-activator CBP, suggesting that COUP-TF functions as an accessory protein for RAR α to induce RAR β promoter transcription. Together, our results demonstrate that COUP-TF is required for RA-dependent RAR β induction, growth inhibition and apoptosis by acting as an accessory protein for RAR α to recruit its co-activator (Figure 2). The facts that COUP-TF is not expressed in many cancer cell lines and that loss of RAR β is an early event in carcinogenesis suggest that COUP-TF may have a role in cancer development.

