Differential Responses of Normal, Premalignant, and Malignant Human Bronchial Epithelial Cells to Receptor-selective Retinoids

Shi-Yong Sun, Jonathan M. Kurie, Ping Yue, Marcia I. Dawson, Braham Shroot, Roshantna A. S. Chandraratna, Waun K. Hong, and Reuben Lotan


ABSTRACT

Using an in vitro lung carcinogenesis model consisting of normal, premalignant, and malignant human bronchial epithelial (HBE) cells, we analyzed the growth inhibitory effects of 26 novel synthetic retinoic acid receptor (RAR)- and retinoid X receptor (RXR)-selective retinoids. RAR-selective retinoids such as CD271, CD437, CD2325, and SR11364 showed potent activity in inhibiting the growth of either normal or premalignant and malignant HBE cells (IC₅₀ mostly <1 μM) and were much more potent than RXR-selective retinoids. Nonetheless, the combination of RAR- and RXR-selective retinoids exhibited additive effects in HBE cells. As the HBE cells became progressively more malignant, they exhibited decreased or lost sensitivity to many retinoids. The activity of the RAR-selective retinoids, with the exception of the most potent retinoid, CD437, could be suppressed by an RAR panantagonist. These results suggest that: (a) RAR/RXR heterodimers play an important role in mediating the growth inhibitory effects of most retinoids in HBE cells; (b) CD437 may act through an RAR-independent pathway; (c) some of the RAR-selective retinoids may have the potential to be used in the clinic as chemopreventive and chemotherapeutic agents for lung cancer; and (d) early stages of lung carcinogenesis may be responsive targets for chemoprevention by retinoids, as opposed to later stages.

INTRODUCTION

The incidence of lung cancer has been increasing in both men and women for the last several decades. Since 1987, lung cancer has been the leading cause of cancer death and accounted for 25% of all cancer deaths in women (1). It has been estimated that there will be 171,500 new cases and 160,100 deaths from lung cancers in the United States in 1998 (1). Unfortunately, the present therapeutic approaches for lung cancer including surgery, radiation therapy, and chemotherapy have not improved the 5-year relative survival rate, which is still only 14% for all patients, regardless of stage at diagnosis. Therefore, new approaches for preventing and treating lung cancer are being explored. One promising approach is chemoprevention and therapy with retinoids (2–4).

Retinoids are a group of natural and synthetic vitamin A analogues that exert profound effects on the proliferation and differentiation of many cell types, including normal, premalignant, and malignant lung epithelial cells, both in vitro and in vivo (5, 6). Retinoids suppress carcinogenesis in diverse epithelial tissues including, skin, oral mucosa, trachea, and lung (5, 6). Clinical trials have demonstrated the efficacy of retinoids in suppressing oral leukoplasia, reducing second upper aerodigestive tract cancers in patients with prior head and neck or lung cancer, and inducing clinical remission of acute promyelocytic leukemia (7–12).

Vitamin A deficiency is associated with the development of squamous metaplasia in the bronchiolar epithelium and is linked to increased susceptibility to lung cancer (3, 4). Retinoids can act on normal bronchial epithelium by inducing mucins and blocking aberrant squamous differentiation (13, 14). Vitamin A and several retinoids prevent lung carcinogenesis in animal models (15, 16). Furthermore, the treatment of patients who had undergone surgical resection of stage I NSCLC with retinyl palmitate reduced the incidence of second primary lung tumors (9). Lung cancer chemoprevention studies with retinoids are aimed to reverse premalignant lesions such as sputum atypia and squamous metaplasia of the bronchial epithelium, prevent an initial lung cancer, and prevent second primary tumors in patients previously treated for lung cancer (4, 9).

The effects of retinoids are believed to be mediated by two...
types of nuclear receptor, RARs and RXRs, which are members of the steroid hormone-receptor superfamily (17–19). Each type of receptor consists of three subtypes that are encoded by three distinct genes designated α, β, and γ. The RARs bind ATRA and 9-cis RA, whereas the RXRs bind only 9-cis RA (17–19). These receptors form RXR-RAR heterodimers and RXR-RXR homodimers, which function as ligand-activated transcription factors that regulate the transcription of target genes by binding to response elements specific for RAR (RAREs) or RXR (RXREs) located in the 5’ upstream region of these genes (17–19).

After the discovery of nuclear retinoid receptors, novel retinoids with different receptor selectivities that can bind RARs or RXRs or that prefer one subtype (e.g., α) to others (e.g., β and γ) have been synthesized and characterized (20–30). The availability of new receptor-selective retinoids raised the possibility that some of them may be more effective against lung cancer cells than RA.

Although ATRA can suppress the growth and squamous differentiation of bronchial epithelial cells (14), this effect is diminished during lung carcinogenesis, and the majority of human lung cancer cell lines are refractory to ATRA in vitro (31, 32). In the present study, we compared and contrasted the effects of different synthetic retinoids on the growth of normal, premalignant, and malignant HBE cells. Using this lung carcinogenesis model, we found that normal HBE cells and early premalignant cells maintained sensitivity to some retinoids; however, they gradually lost their sensitivity to many retinoids. This study indicates that some of the retinoids may have potential use as chemopreventive agents for lung cancer and suggests that the target for lung cancer chemoprevention with retinoids should be early stages of lung carcinogenesis.

MATERIALS AND METHODS

Cells and Cell Culture. A lung carcinogenesis model that includes normal, premalignant, and malignant HBE cells was used in this study. NHBE cells were prepared from bronchial epithelium harvested from fresh surgical specimens obtained from patients undergoing lobectomy procedures, as described previously (32). For the purpose of this study, premalignant cell lines were defined as immortalized non-tumorigenic cells, and malignant cell lines were defined as immortalized tumorigenic cells. The premalignant cell lines 1799 and 1198 and malignant cell line 1170-I were obtained from Dr. Klein-Szanto (Fox Chase Cancer Center, Philadelphia, PA; Ref. 33). The characteristics of these cell lines are summarized in Table 1 and have been described in detail previously (32). The NHBE cells and the 1799 cells grow in Keratinocyte Serum-Free Medium (Life Technologies, Inc., Gaithersburg, MD) containing epidermal growth factor and bovine pituitary extract (34), whereas 3% serum is required for the growth of premalignant 1198 and malignant 1170-I cells (33). Cells were grown on tissue culture plasticware (Falcon; Becton Dickinson, Bedford, MA) at 37°C in a humidified atmosphere composed of 95% air and 5% CO₂. Soybean trypsin inhibitor (Sigma Chemical Co., St. Louis, MO) was added to the culture medium. For the growth inhibition assay, NHBE cells and 1799 cells were cultured in medium with 0.09% BSA in the absence of epidermal growth factor.

Retinoids. ATRA, 9-cisRA, 13-cisRA, Am80, and TTNN were obtained from Dr. Werner Bollag (F. Hoffmann-La Roche, Basel, Switzerland). The retinoids CD270, CD271, CD336, CD437, CD666, CD2314, CD2325, CD2366, and CD2665 were synthesized by CIRD/Galderma (Sophia Antipolis, France; Refs. 20 and 24). The retinoids SR3985, SR11203, SR11217, SR11234, SR11236, SR11238, SR11254, SR11363, and SR11364 were synthesized in the laboratory of Dr. M. I. Dawson (22, 28, 29). LG1069 was obtained from Dr. Richard Heyman (Ligand Pharmaceuticals, San Diego, CA; Ref. 27). 4HPR was obtained from Dr. Ronald Lubet (National Cancer Institute, Bethesda, MD). AGN193109 was provided by Dr. R. A. S. Chandraratna (Allergan Inc., Irvine, CA; Ref. 35). The retinoids SR3985, SR11203, SR11217, SR11234, SR11236, SR11238, SR11254, SR11363, and SR11364 were synthesized in the laboratory of Dr. M. I. Dawson (22, 28, 29). LG1069 was obtained from Dr. Richard Heyman (Ligand Pharmaceuticals, San Diego, CA; Ref. 27). 4HPR was obtained from Dr. Ronald Lubet (National Cancer Institute, Bethesda, MD). AGN193109 was provided by Dr. R. A. S. Chandraratna (Allergan Inc., Irvine, CA; Ref. 35). The chemical structure and receptor affinity or transactivation activity of these retinoids have been described previously (36). All of the retinoids were dissolved in DMSO at a concentration of 10⁻³ M and stored in the dark at −80°C under N₂. Stock solutions were diluted to the appropriate final concentrations in growth medium just before use.

Cell Treatment with Retinoids and Determination of Growth Inhibition. Cells were seeded at densities ranging from 1 x 10³ to 5 x 10³ cells/well in 96-well cluster tissue culture plates. After 24 h, the cells were treated with different concentrations of the retinoids. Control cultures received the same amount of DMSO as the treated cultures did. Cells were treated again with fresh retinoids on day 4. On day 7, cell numbers were estimated by using the sulforhodamine B assay, as described previously (36). Four replicate wells were used for each analysis. The percentage of GI was calculated by using the...
equation: \( \%\text{ GI} = (1 - \text{Nt/Nc}) \times 100 \), where \( \text{Nt} \) and \( \text{Nc} \) represent the absorbance in treated and control cultures, respectively. The drug concentration required to cause 50% cell growth inhibition (IC\(_{50}\)) was determined by interpolation from dose-response curves.

RESULTS

Differential Responses of Normal, Premalignant, and Malignant HBE Cells to Synthetic Retinoids. Some characteristics of the four cell lines, including normal, premalignant, and malignant HBE cells, which constitute an in vitro lung carcinogenesis model, are presented in Table 1. We first compared the responses of these cell lines to 26 different synthetic retinoids, including RAR-selective agonists and antagonists, and RXR-selective and anti-AP-1 compounds. Fig. 1, A-D, and Table 2 show the effects of 26 retinoids in the above cell lines. ATRA, 9-cis RA, 13-cis RA, 4HPR, and LG1069 are presently used for cancer treatment and prevention in clinical trials. Their effects are shown in Fig. 1A and Table 2. ATRA, 9-cis RA, and 13-cis RA, showed weak growth inhibitory effects that were more pronounced in the NHBE cells and the immortalized 1799 cells than in the more progressed cell lines. 4HPR and LG1069 were more potent than the natural RAs and affected all cell lines when used at 10 \( \mu\text{M} \) (both retinoids). 4HPR was more potent than the RXR-selective retinoid LG1069 and inhibited the growth of both NHBE and 1799 cells even at 1 \( \mu\text{M} \), whereas LG1069 was ineffective at this concentration.

In general, RAR-selective retinoids were much more active in inhibiting cell growth than RXR-selective retinoids (Fig. 1, B-D, and Table 2). The majority of RAR-selective retinoids showed concentration-dependent growth inhibitory effects that were similar to those of 4HPR, but some of them (such as CD271, CD437, CD2325, and SR11364) were much more active than 4HPR (Fig. 1, B and C). Interestingly, the RAR-selective retinoids with the most potent growth inhibitory activity were those with RAR\(\gamma\)- or RAR\(\beta/\gamma\)-selectivity such as CD271, CD437, CD2325, SR3985, SR11363, and SR11364. The RAR\(\beta\)-selective retinoid CD2314 and the RAR\(\beta/\gamma\)-selective TTNN had potent growth-inhibitory effects in NHBE and 1799 cells, but exhibited either decreased or no activity in 1198 and 1170-I cells (Fig. 1C). The RAR\(\gamma\)-selective retinoids Am80 and CD336 as well as two other RAR\(\gamma\)-selective ones, CD666 and SR11254, showed relatively weak activities, which were similar to that of ATRA.

RXR-selective retinoids exhibited very weak activity in inhibiting the growth of the different cell types (Fig. 1D and Table 2). SR11217 was relatively more active than the other RXR-selective retinoids, but at high concentrations this com-
Table 2  Effects of different retinoids on the growth of normal, premalignant, and malignant HBE cells

<table>
<thead>
<tr>
<th>Compound</th>
<th>RAR/RXR selectivity</th>
<th>NHBE</th>
<th>1799</th>
<th>1198</th>
<th>1170-I</th>
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<tr>
<td>eFGF</td>
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<td>6.80</td>
<td>2.30</td>
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<td>FGF</td>
<td>RARα</td>
<td>&gt;10</td>
<td>0.113</td>
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<td>CD2314</td>
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<td>1.45</td>
<td>1.39</td>
<td>7.60</td>
<td>7.25</td>
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<tr>
<td>TTNN</td>
<td>RARβ and γ</td>
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<td>0.56</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD270</td>
<td>RARβ and γ</td>
<td>4.65</td>
<td>0.45</td>
<td>5.95</td>
<td>5.80</td>
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<tr>
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<td>0.162</td>
<td>0.175</td>
<td>0.22</td>
<td>0.24</td>
</tr>
<tr>
<td>SR3985</td>
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<td>2.00</td>
<td>0.16</td>
<td>2.20</td>
<td>1.94</td>
</tr>
<tr>
<td>CD2665⁴</td>
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<td>0.31</td>
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<td>3.0</td>
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<td>CD666</td>
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<td>0.183</td>
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<td>3.95</td>
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<td>&gt;10</td>
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<td>SR11363</td>
<td>RARγ</td>
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<td>CD2366⁵</td>
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<td>7.00</td>
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<tr>
<td>ATRA</td>
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<tr>
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<td>2.70</td>
<td>&gt;10</td>
<td>&gt;10</td>
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<tr>
<td>LG1069</td>
<td>RXR</td>
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<td>2.50</td>
<td>3.75</td>
<td>3.35</td>
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<tr>
<td>9-ciRA</td>
<td>RAR and RXR</td>
<td>&gt;10</td>
<td>0.030</td>
<td>&gt;10</td>
<td>&gt;10</td>
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<tr>
<td>SR11238⁶</td>
<td>SFR and RXR</td>
<td>&gt;10</td>
<td>0.013</td>
<td>&gt;10</td>
<td>&gt;10</td>
</tr>
<tr>
<td>13-ciRA</td>
<td>SFR</td>
<td>&gt;10</td>
<td>0.013</td>
<td>&gt;10</td>
<td>&gt;10</td>
</tr>
<tr>
<td>4HPR</td>
<td>SFR</td>
<td>0.23</td>
<td>0.131</td>
<td>2.0</td>
<td>1.75</td>
</tr>
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</table>

⁴ Cell treatment and GI assay are described in detail in “Materials and Methods.”
⁵ Defined as having more than 30% GI at 10µM.
⁶ Defined as having less than 30% GI at 10 µM.
⁷ RAR antagonists.
⁸ Anti-AP-1 activity.
⁹ 13-ciRA can be isomerized to AT RA, which binds RARs.
⁰ 4HPR, though unable to bind to RARs, has been found to transactivate RARE in certain cells (47, 48).

The HBE cells showed decreased sensitivity to most of the retinoids, except for CD437, as they progressed from normal to malignant cells (i.e., from NHBE to 1170-I; Fig. 1D and Table 2). Of these cells, early premalignant 1799 cells that were not exposed to CSC in the process of their isolation (33) were the ones most sensitive to many of the retinoids.

Effects of RAR-selective Antagonists Alone and in Combination with Some RAR Agonists. Surprisingly, at concentrations of 1 µM or higher, the antagonist RARα/β/γ-selective (CD2366) and RARβ/γ-selective (CD2665) retinoids inhibited the growth of the HBE cells (Fig. 1C and Table 2). Apparently, in these cells, these antagonists act as partial agonists. In contrast, the RAR α/β/γ-selective antagonist AGN193109 (35) failed to inhibit the growth of the HBE cells (Fig. 2). Therefore, we used the latter antagonist to determine whether it could repress the action of the agonistic retinoids. Because we wanted the concentration of the antagonist AGN193109 to be in excess relative to agonists, we use the more sensitive NHBE and 1799 cells in which lower concentrations of agonists (e.g., 0.5 µM) were effective. As shown in Fig. 2, the growth inhibitory effects of CD271, CD2325, and SR11364 were diminished by 2.5 µM AGN193109 in both NHBE and 1799 cells. The growth inhibitory effects of CD666, Am80, CD270, ATRA, and 9-ciRA were partially antagonized by AGN193109 in 1799 cells. These results indicated that RARs play a role in the pathway involved in GI. As an exception, a 25-fold excess concentration of AGN193109 failed to antagonize the growth inhibitory effects of CD437 in NHBE and 1799 cells, suggesting that CD437 may have a unique mechanism distinct from the RAR pathway, as previously suggested by others (30) and ourselves (37).

Enhanced Growth Inhibitory Effects of RAR-selective Retinoids Combined with RXR-selective Ones. RXR/RAR heterodimers are believed to be the major mediators of the effects of retinoids on gene expression (38, 39). The combination of RAR- and RXR-selective retinoids exhibited additive or synergistic activity in some cell lines (40, 41). Therefore, we analyzed the combined effects of RAR- and RXR-selective retinoids at 5 µM each, which did not give more than 30% GI, in premalignant and malignant HBE cells. As shown in Fig. 3, additive or supra-additive growth inhibitory effects were observed when each of five RAR-selective retinoids was combined with each of three RXR-selective ones, respectively, in 1198 and 1170-I cells. The combination of RARβ-selective (CD2314), RARγ-selective (SR11363), and RARβ/γ-selective (CD270) retinoids with three RXR-selective retinoids exhibited...
clear additive growth inhibitory effects in both cell lines, whereas the RARα-selective retinoid CD336 and the pan-RAR-selective ATRA showed only modest additive growth inhibitory effects when combined with some RXR-selective retinoids. These results provide indirect evidence to support a role for RXR/RAR heterodimers in mediating the growth inhibitory effects of retinoids and suggest that RARβ and/or RARγ play a more important role than RARα in the heterodimer pathway mediating GI.

DISCUSSION

Carcinogenesis is considered to be a multistep process involving initiation, promotion and progression (42). The exposure of tissue to carcinogenic and tumor-promoting agents often leads to histological changes over large areas of the tissue (e.g., aerodigestive tract epithelium), resulting in a “field cancerization” with potential multifocal unsynchronized, premalignant and primary malignant lesions. Chemoprevention, which targets the multistep process of carcinogenesis with chemical agents that delay, reverse, or block cancer development, is one of the novel and potentially effective approaches to cancer control (43). The cell lines used in this study consisted of normal, premalignant and malignant HBE cells, among which the premalignant (1799 and 1198) and malignant (1170-I) cells evolved from the same precursor cells (32). This precursor cell, BEAS-2B, underwent the series of steps required to proceed from an immortalized HBE cell to a fully malignant cell as represented by the different cell types derived from the xenograft model (1799), exposure to CSC (1198), and transformation from an immortalized to a malignant cell (1170-I; Ref. 33). Therefore, this group of cell lines is a useful in vitro carcinogenesis model in which to screen and study chemopreventive agents, especially those relevant for lung cancer.

The four cell lines exhibited different responses to retinoid treatment. The 1799 premalignant cells were relatively sensitive to the majority of the tested retinoids and were even more sensitive than normal HBE cells to some retinoids. The cells decrease or lose their responsiveness to retinoid treatment as they progress from normal (NHBE) and early premalignant cells (1799) to late premalignant (1198) and fully malignant cells (1170-I). Geradts et al. (31) and our previous study (36) revealed that human lung cancer cells exhibited resistance to ATRA and many synthetic retinoids. Therefore, our present results clearly indicate that lung epithelial cells at early premalignant stages would be suitable targets for lung cancer chemoprevention by retinoids. Among these retinoids, a few such as CD437, CD2325, CD271, and SR11364 were very active in inhibiting all four HBE cell lines, although their efficacies also decreased as the HBE cells became progressively more malignant. Our previous study also found that these retinoids, especially CD437, were effective in inhibiting the growth of human NSCLC cells (36). Therefore, these retinoids may have the clinical potential as chemopreventive and therapeutic agents against lung cancer.
RARs (α, β, and γ) and RXRs (α, β, and γ) are believed to mediate most of the effects of retinoids on the gene expression associated with modulating cell growth and differentiation. RARs require heterodimerization with RXRs for effective DNA binding and function (18, 19, 44, 45), whereas RXRs can form either RXR/RXR homodimers or RXR/RAR heterodimers in the presence of 9-cisRA (46). Thus, heterodimers and homodimers represent two distinct pathways of signaling by retinoids. On the basis of the results obtained from this HBE carcinogenesis model, we find that RAR-selective retinoids are much more active than RXR-selective ones in inhibiting the growth of HBE cells. The unexpected finding that the RAR antagonists CD2665 and CD2366 inhibited growth at high concentrations may be explained by their acting as partial agonists at those concentrations. The RAR-specific panantagonist AGN193109, which has high binding affinity to RARs but does not have transactivating activity (35), partially or completely suppressed the growth inhibitory effects of some representative retinoids. Therefore, we conclude that nuclear retinoid receptors play a role in mediating growth inhibitory effects of some of the retinoids and the RXR/RAR heterodimer, rather than RXR/RXR homodimer-mediated pathway, plays an important role in GI of HBE cells.

Recently, it has been reported by Westin et al. (47) that the binding of an RAR-selective ligand to RAR and of an RXR-selective ligand to RXR in the same RXR/RAR heterodimers can enhance the binding of a coactivator (e.g., SRC-1), and this may explain the additive or synergistic effects of the combination of retinoids. Therefore, the result that the combination of RAR-selective and RXR-selective retinoids exhibited additive or synergistic growth inhibitory effects in HBE cells also supports the role of RXR/RAR in these effects. In addition, the combination of RAR-selective CD270 or SR11263 and RXR-selective LG1069, which is used as single agent in present clinical trials, may be useful in clinical trials for cancer prevention and treatment.

Most retinoids with RARγ selectivity were more potent than the other retinoids in inhibiting the growth of HBE cells. Even the potent 4HPR was recently reported to activate RARE via RARγ in some cell systems (48, 49). Therefore, we suggest that RARγ could be the major receptor in the RXR/RAR heterodimer pathway that mediates the growth inhibitory effects of retinoids in normal, premalignant, and malignant HBE cells.

CD437, an RARγ-selective retinoid, was the most active among all of the retinoids used in this study in inhibiting the growth of all stages of HBE cells. Unlike other retinoids, its growth inhibitory effects could not be suppressed even by the RAR panantagonist AGN193109. This suggests that the mechanism by which CD437 exerts its growth inhibitory effect in HBE cells may be independent of the RAR-mediated pathway and is consistent with recent observations by others in human breast cancer cells (30), and ourselves in lung cancer cells (37), that CD437 induces apoptosis by a RAR-independent mechanism.

One way by which RARs regulate gene expression is by antagonizing the action of AP-1 (50). Retinoids possessing anti-AP-1 activity have been shown to inhibit the growth of some tumor cells (28). However, none of the four HBE cell lines used responded to the reported anti-AP-1 retinoid SR11238. In our previous study, eight human NSCLC cell lines did not respond to this compound, either (36). It is possible that anti-AP-1 activity is not a general molecular mechanism of the antiproliferation effects of retinoids.

In conclusion, we have demonstrated that several synthetic receptor-selective retinoids are more potent than the RAs in inhibiting the growth of HBE cells and that their action is mediated by retinoid receptors, presumably through RXR/RAR heterodimers. The use of the lung carcinogenesis model enabled us to propose that early stages of lung carcinogenesis may be the more responsive targets for chemoprevention by certain of the active retinoids identified here, as opposed to later stages.

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