Breast Cancer
R E S E A R C H

EDITORIAL

Retinoids and breast cancer: new clues to increase their activity and selectivity

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Abstract

All-trans retinoic acid and derivatives (retinoids) are promising agents in the management of certain hematologic malignancies and solid tumors, including breast cancer. Retinoids are endowed with anti-proliferative, cyto-differentiating and apoptotic effects that are largely mediated by activation of the nuclear hormone retinoic acid receptors RARα, RARβ and RARγ. These are ligand-dependent transcriptional factors controlling the expression of numerous genes. The relative importance of each receptor subtype for the anti-tumor activity of retinoids is largely unknown. Clarification of this point is of fundamental importance for the rational design of retinoid-based therapeutic approaches aimed at controlling a heterogeneous type of tumors, like breast cancer.

The results presented by Bosch and colleagues [1] in the previous issue of *Breast Cancer Research* are a major step towards the identification of the critical determinants controlling the responses of breast tumor cells to all-trans-retinoic acid (ATRA), the prototype of retinoids, a promising class of anti-cancer agents. The authors demonstrate that the two retinoid nuclear receptors RARα and RARγ play opposite roles in controlling the growth of breast cancer cells [1]. Retinoid-dependent activation of RARα arrests the growth, while activation of the other receptor favors the proliferation of the neoplastic cell. Suppression of RARγ activity enhances the antiproliferative effects of ATRA in cultures of breast cancer cell lines and in an appropriate animal model of the tumor. Finally, the RARα agonist AM580 [2] is more effective than the pan-RAR ligand, ATRA [3,4], in controlling the growth of breast cancer cells both *in vitro*

and *in vivo*. This is consistent with the intrinsic ability of ATRA to activate RARα and RARγ simultaneously.

ATRA is the only example of a clinically useful cyto-differentiating agent in oncology [3,4], having changed the natural history of acute promyelocytic leukemia, a rare form of acute myelogenous leukemia [5]. This along with promising results obtained in preclinical models has spurred interest in the use of ATRA and natural (9-*cis* and 13-*cis* retinoic acid) or synthetic derivatives (retinoids) also for the management of solid tumors, with particular reference to breast cancer. However, the clinical experience accrued with ATRA and derivatives in breast cancer has not kept up with expectations [6]. Indeed, so far, promising results have been obtained only with the atypical synthetic retinoid fenretinide, which is effective in the secondary prevention of pre-menopausal breast tumors [7].

One of the reasons for the poor clinical outcome of ATRA in breast cancer may be linked to the heterogeneity of this tumor, which is a collection of distinct entities with different biological and prognostic characteristics [8]. Thus, the identification of specific markers defining breast cancer subtypes with particular sensitivity to ATRA and derivatives is likely to represent a priority in studies aimed at developing rational therapeutic approaches based on the use of these compounds. Definition of RARα and RARγ as a positive and a negative determinant of retinoid sensitivity in breast carcinoma [1] is an important step in this direction. In fact, it suggests that breast tumors with high RARα/RARγ ratios should represent optimal targets for retinoids. Two large subgroups of breast cancer with these characteristics have been identified. The first one is represented by estrogen receptor-positive tumors, where estrogens are known to increase the activity of *RARA*, the gene encoding RARα, while leaving unaffected the RARγ-encoding counterpart [9,10]. The idea is supported by the observation that estrogen receptor-positive breast carcinoma cell lines are sensitive to ATRA, while estrogen receptor-negative ones are not [11]. A second subgroup characterized by high RARα/RARγ ratios has been identified among Her2/*neu*-positive breast cancers [12]. In fact,

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approximately 20 to 25% of Her2/*neu*-positive tumors have been shown to present with co-amplification of the *RARA* gene, with consequent high constitutive levels of the encoded receptor. Cell lines recapitulating this genotype are characterized by sensitivity to ATRA-dependent anti-neoplastic activity, regardless of the estrogen-receptor status [12] and sensitivity is mediated by RARα. Despite what has been discussed above, the search for tumor subtypes with high RARα/RARγ ratios may be an oversimplification of the problem. In fact, RARs are not the only nuclear receptors activated by ATRA, which has been demonstrated to stimulate peroxisome proliferator-activated receptor (PPAR)β/δ as well [13]. Interestingly, ATRA-dependent activation of PPARβ/δ is also associated with increased breast cancer cell growth, which is similar to what has been observed for RARγ [14]. This adds a further layer of complexity to the search for breast tumor subtypes that may benefit from retinoid treatment.

The work of Bosch and colleagues supports the concept that RARα is the principal mediator of ATRA anti-tumor activity in breast cancer. The authors propose that targeting of RARα with selective agonists, like AM580, may be a more effective clinical strategy to hit breast cancer cells than a pan-RAR agonist like ATRA. Indeed, the proposed therapeutic strategy may have additional value besides the observed lack of RARγ activation. The use of RARα agonists should theoretically avoid activation of RARβ, whose expression in tumor-associated stromal cells is a potential determinant of breast cancer growth [15]. In addition, selective targeting of RARα may reduce certain aspects of retinoid systemic and dose-limiting toxicity, such as skin rashes and intra-cranial hypertension [3,4], two effects that are believed to be mediated by RARγ. However, simple activation of RARα may not be an optimal strategy to counter breast cancer growth and progression, as such an approach does not take into consideration the circulating levels of endogenous ATRA (1 to 10 nM) that are sufficient to activate tumor cells' RARγ. Hence, we propose that approaches based on combinations between RARα agonists and RARγ antagonists may represent a more rational strategy in the clinical management of breast cancer.

In conclusion, the work of Bosch and colleagues revives interest in retinoids for the treatment and chemo-prevention of breast cancer. A rational use of these agents calls for more in-depth knowledge of the molecular mechanisms and determinants underlying the sensitivity/resistance of the neoplastic cell to ATRA and derivatives. This is likely to result in the development of effective therapeutic protocols based on combinations between retinoids and other anti-neoplastic agents, which is the ultimate goal of this line of research.

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