MiniReview

Nuclear Receptors as Modulators of the Tumor Microenvironment

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Abstract

Over the past several decades of cancer research, the inherent complexity of tumors has become increasingly appreciated. In addition to acquired cell-intrinsic properties, tumor initiation and growth is supported by an abundance of parenchymal, inflammatory, and stromal cell types, which infiltrate and surround the tumor. Accumulating evidence shows that numerous components of this supportive milieu, referred to collectively as the tumor microenvironment, are indeed critical during the process of multistep tumorigenesis. These findings highlight the important interplay between neoplastic cells and tumor-associated cell types, and suggest that therapy should target both neoplastic cells and supportive stromal cells to effectively attenuate tumor growth. The nuclear receptor superfamily encompasses a druggable class of molecules expressed in numerous stromal and parenchymal cell types, whose established physiologic roles suggest their potential as therapeutic and preventive targets in the context of the reactive tumor microenvironment. In this minireview, we discuss recent evidence that tumor-associated inflammation, angiogenesis, and fibrosis can be modulated at the transcriptional level by nuclear receptors and their ligands. As these processes have been widely implicated in cancer initiation, progression, and resistance to current therapy, nuclear receptor ligands targeting the tumor microenvironment may be potent antitumor agents in combination therapies, including for preventing cancer development within high-risk populations. *Cancer Prev Res; 5(1); 3–10. ©2011 AACR.*

Introduction

Solid tumors are no longer viewed simply as clonal expansions of cancer cells. Instead, the current view of the tumorigenic process posits that a tumor is a complex cellular expansion consisting of heterogeneous and ever-evolving cancer cells, as well as their coevolving microenvironment (1, 2). Although alterations in the tumor cell genome have long been thought to drive tumor initiation and progression, the strong influence of nonmalignant cells of the microenvironment on tumor development and growth has been more recently appreciated and is only now beginning to be understood (3). Indeed, solid tumors have come to be defined in part as complex networks of tumor cells in paracrine communication with cells of the microenvironment, including resident fibroblasts, endothelial cells, pericytes, and leukocytes, which serve critical functions in helping the cancer cells meet myriad requirements for their

survival (4, 5). For example, release of secreted factors such as TGF-β (6, 7), stromal cell–derived factor 1 (8), and hepatocyte growth factor (9) by stromal fibroblasts has been shown to modulate the oncogenic and metastatic potential of adjacent epithelial tissues. Activated cancer-associated fibroblasts also deposit extracellular matrix (ECM) components that contribute to tumor cell survival and chemoresistance (10–12). In addition, activation of *de novo* angiogenesis supplies tumor cells with needed nutrients and oxygen, and it is mediated by local stimulation of vascular endothelial cells with pro- and antiangiogenic factors such as VEGF-A and thrombospondin-1 (TSP-1), respectively (13, 14); recruitment of vasculature-supporting pericytes (15) also aids the process of tumor-associated angiogenesis. Together, such tumor-derived factors activate the "angiogenic switch" characteristic of most neoplastic growths—activation of this process, normally dormant in adults, supports tumor growth as well as invasion and metastasis.

Infiltrating leukocytes of the innate and adaptive immune systems also populate the tumor microenvironment, and it has become increasingly apparent that each stage of cancer development is susceptible to regulation by immune cells (16, 17). Infiltrating immune cells engage in a complex cross-talk with tumor cells and other cell types of the tumor microenvironment via both protumorigenic and antitumorigenic mechanisms. Indeed, the same immune or inflammatory cell subtype may exhibit both protumorigenic and antitumorigenic functions. Depending on

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differentiation status and the presence of TGF-β, neutrophils, for example, show tumor-directed cytotoxicity as well as regulation of cytotoxic T lymphocyte responses in certain contexts and in others produce cytokines, proteases, and reactive oxygen species (ROS) that promote tumor growth (18). Tumor-associated macrophages (TAM) are frequently found in the tumor microenvironment, and recent evidence suggests that the M2 macrophage subtype, commonly characteristic of TAMs, can produce cytokines which promote tumor angiogenesis and tissue remodeling as well as cytokines such as interleukin 10 (IL-10) with tumor-suppressive potential (19, 20). As tumor cells exhibit a remarkable dependence on their microenvironment for growth, the cell types and pathways therein may represent valuable targets for therapy.

Nuclear receptors (NR) are a superfamily of ligand-activated transcription factors that regulate development, cellular differentiation, reproduction, and metabolism of lipids, drugs, and energy (21). As intracellular sensors of lipophilic hormones, vitamins, dietary lipids, or other stimuli, NRs act as transcriptional switches to orchestrate responses to environmental cues at the level of gene expression (22). Genomic sequence availability has led to the identification of 48 NRs encoded by the human genome and 49 NRs encoded by the mouse genome (23–25). In addition to normal metabolic and homeostatic processes, NRs are important regulators of various disease states including diabetes, obesity, atherosclerosis, and cancer (26, 27). The appreciated roles of various NRs in controlling proliferation, differentiation, and apoptosis are suggestive of direct antitumor effects for NRs and their ligands on cancer cells, as has been shown in numerous contexts. However, less attention has been paid to the putative therapeutic value of NRs and their ligands in the tumor microenvironment, where regulation by NRs of such processes as fibrosis, angiogenesis, and inflammation may complement cancer cell–targeted chemotherapy to blunt tumor growth.

Although our understanding of the dynamic and extensive interactions between tumor cells and their surroundings remains incomplete, it seems clear that targeting both neoplastic cells and the stromal elements needed for their survival represents a promising avenue for cancer prevention and therapy. Indeed, antiangiogenic strategies for cancer treatment are currently in place (28) and under steady development (29) for use in human patients, whereas endogenous inhibitors of angiogenesis have yielded promising results in mouse models of cancer (30). Compounds targeting inflammation and/or inflammatory immune cell types have also shown encouraging antitumor effects (31). Several nonsteroidal anti-inflammatory drugs are appreciated anticancer agents (32), particularly the highly selective COX-2 inhibitors (33, 34), in part, because of their antiangiogenic properties. Accordingly, daily aspirin use has been shown to reduce the risk of developing several common cancer types (35–38). In addition, recent work has shown the utility of CD40 agonists in mice and humans to relieve immune suppression and promote tumoricidal T-cell activity (39–41) or to activate macrophages in a manner that promotes tumor cell killing and depletion of tumor stroma, leading to tumor regression even independent of chemotherapy (42). Similarly, ablation of cancer-associated fibroblasts in several mouse models of cancer, via fibroblast activation protein-targeted vaccination (43) or genetic engineering (44), has been shown to reduce matrix deposition, improve chemotherapeutic drug uptake, and relieve local immune suppression, leading to a reduction in tumor burden. Together, these studies underscore the therapeutic potential of cancer treatment strategies targeting stromal cell types. Expressed in numerous stromal cell types and implicated in multiple cancer-related processes, NRs represent a frequently druggable class of molecules with the intriguing potential to modulate the tumor microenvironment.

Cancer-Associated Fibroblasts and Related Stromal Elements

Cancer-associated fibroblasts or stromal elements produce hormones, growth factors, cytokines, and other factors which may act in a paracrine manner to influence tumor initiation and progression. NRs in various contexts may act to inhibit these tumor-promoting functions of stromal cells. In the pancreas, carcinogenesis is associated with the trans-differentiation of stromal cells called pancreatic stellate cells (PSC) to a myofibroblast-like phenotype (45). PSCs are the main cell type causing the desmoplastic reaction, a dramatic increase in connective tissue or stroma which infiltrates and surrounds the tumor. Desmoplastic stroma is a defining feature of pancreatic ductal adenocarcinoma, the most common form of pancreatic cancer (46), and contributes to tumor growth, angiogenesis, invasion, and resistance to therapy (47, 48). Quiescent PSCs act as retinol-storing cells with a limited secretome, whereas activated PSCs in the desmoplastic stroma produce a vast array of secreted proteins implicated in fibrosis, proliferation, cell survival, and wound healing (49). This contrast suggests that restoration of the quiescent PSC phenotype may disrupt PSC–tumor cell communication and impair tumor growth. As retinol stores characterize quiescent PSCs and are lost upon activation, the ability of various forms of retinoic acid (RA) to promote PSC quiescence was investigated. Indeed, treatment of PSCs with RA results in activation of RA receptor β (RARβ) and induction of the quiescent state (Fig. 1). This led to reduced Wnt–β-catenin signaling in adjacent cancer cells, reduced motility, decreased ECM deposition, and slowing of tumor progression (50). Similar effects on stellate cell activation state have been observed by treatment of closely related hepatic stellate cells (HSCs) with 1,25-$(OH)_2D_3$, or calcitriol, the active form of vitamin D (51). Subsequent vitamin D receptor (VDR) activation led to decreased HSC proliferation and profibrotic marker expression and to decreased liver fibrosis *in vivo*. These effects highlight the potential utility of VDR ligands in the reversal of premalignant conditions such as hepatic fibrosis (Fig. 2)

Figure 1. Sites of action of ligand-activated nuclear receptors in the tumor microenvironment.
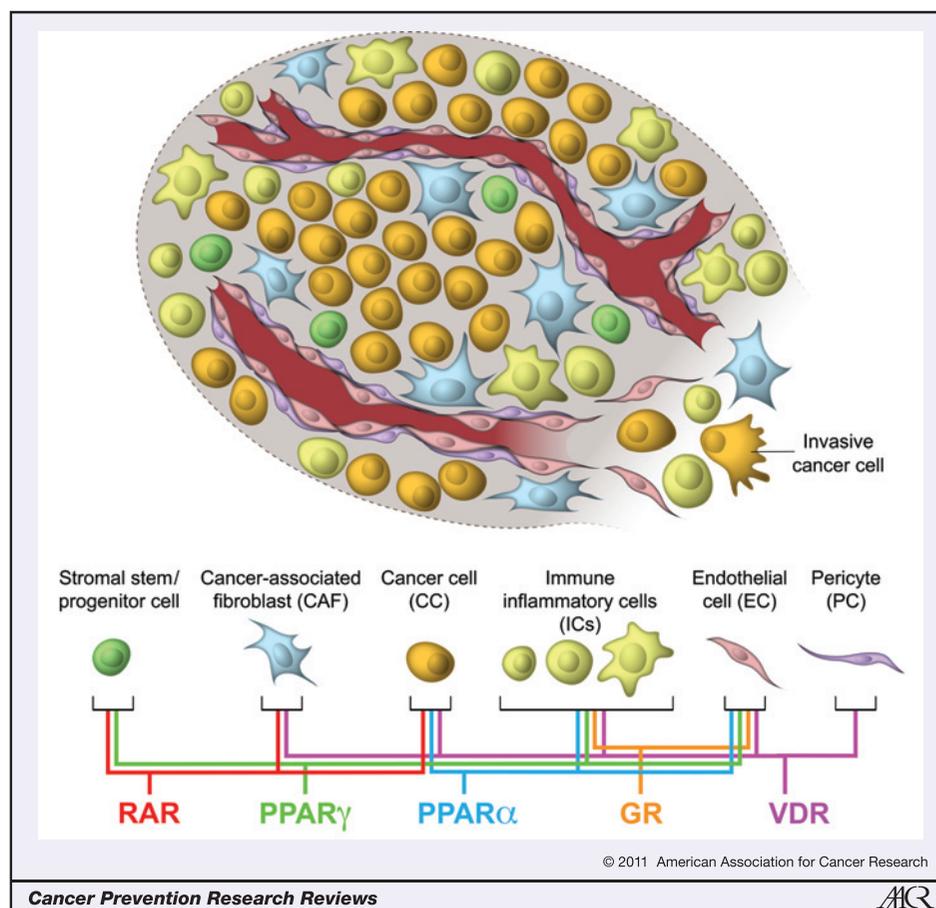
and suggest that these ligands may be of value in targeting PSCs in the pancreatic cancer microenvironment.

In the context of breast cancer, stromal tissue also contributes to tumorigenesis and therefore represents a potentially important therapeutic target. In particular, stromal adipose tissue–produced estrogen plays a key role in breast tumor development and progression, highlighting the importance of communications between stromal tissue and tumor cells in the breast cancer microenvironment. The enzyme aromatase (CYP19) catalyzes the synthesis of estrogens from androgenic precursors, and aromatase is expressed in various tissues including ovary, placenta, bone, brain, and adipose tissue (52, 53). Aromatase expression in these different tissues is under the control of tissue-specific promoters and is differentially regulated by various transcription factors (54). In patients with breast cancer, estrogen levels within the breast tissue are substantially higher than serum levels, indicating local synthesis and accumulation of estrogens that can drive breast cancer growth (55). As such, aromatase inhibitors (AI) have become widely used therapeutic agents to prevent the progression or recurrence of breast cancer after primary therapy (56) and recently have been shown to be effective breast cancer prevention (57)—however, as AIs act to inhibit estrogen synthesis globally, their use can be associated with detrimental side effects in tissues which require estrogen for normal function, such as

bone (58). Selective compounds which inhibit aromatase expression in the breast but permit estrogen synthesis at other sites are therefore desirable for breast cancer therapy. Several NR ligands have been shown to inhibit the aromatase promoter in a tissue-specific manner. Ligands for peroxisome proliferator-activated receptor γ (PPARγ), such as thiazolidinediones (59), and for the retinoid X receptor, such as the synthetic ligand LG101305 (60), have been shown to inhibit the aromatase promoter in breast adipose stromal tissue. These compounds exhibit specificity for aromatase promoter II, a critical regulatory region in mammary adipose tissue, over the bone-specific promoter I.4 (60). The VDR ligand calcitriol has also been shown to specifically inhibit the aromatase promoter in breast stromal adipose as well as breast cancer cells, while paradoxically increasing aromatase expression in bone (61). Unlike breast cancer, the growth of prostate epithelial cells can be negatively affected by estrogens; specifically, estrogen receptor β (ERβ) activity has been shown to promote differentiation while opposing proliferation in the developing prostate (62), and an ERβ agonist has been shown to promote apoptosis in both the stroma and epithelium of benign prostatic hyperplasia and prostate cancer, even in the context of androgen independence (63). Although the precise mechanisms remain to be determined, it was reported that the beneficial impact of ERβ on prostate
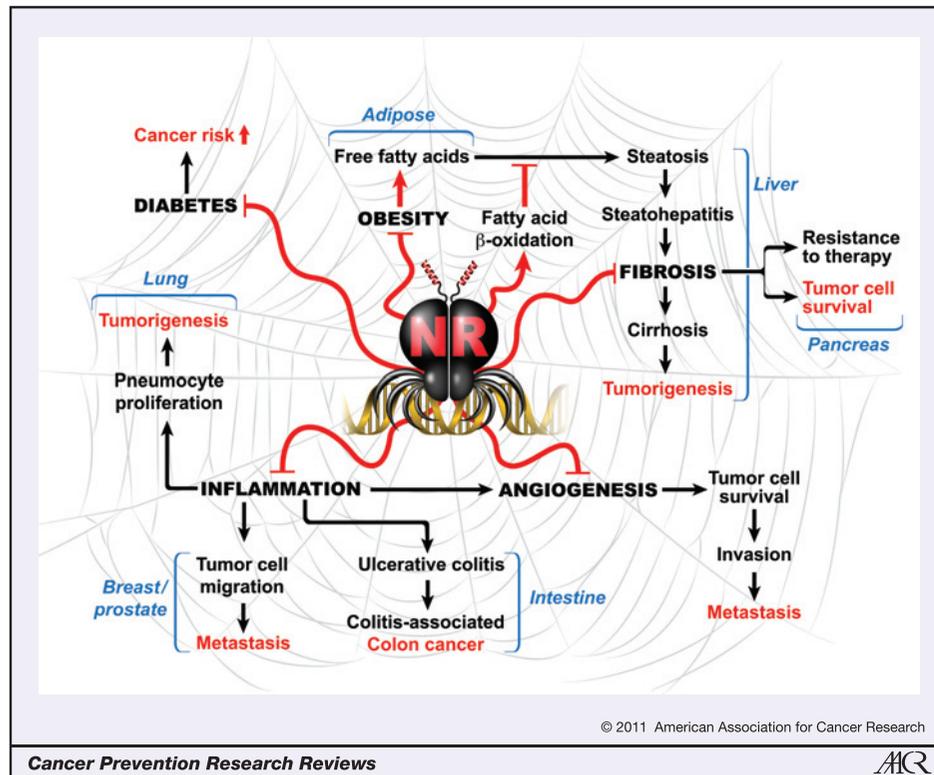
Figure 2. Interrelatedness of nuclear receptors and physiologic or pathologic processes connected to cancer.

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cancer required intraprostatic stromal–epithelial cell signaling, suggesting the importance of the tumor microenvironment in harnessing the therapeutic value of an ERβ ligand.

In addition to fibroblasts and adipose tissue, bone marrow–derived mesenchymal stem cells (MSC) are recruited, as suggested recently, to the stroma of developing tumors (64), where they have been shown to increase tumor incidence, size, and metastatic potential (65). The molecular mediators of MSC–tumor cell communication are therefore intriguing targets for therapy. Among them, MSC-secreted chemokine (C-C motif) ligand 5 (CCL5, also called RANTES) was shown to be required for MSC-induced effects on metastasis in breast cancer, although this depends upon breast cancer cell type (66). Impairing the interaction between MSC-produced CCL5 and CC receptor 5, its receptor, on the surface of breast cancer cells may be an exciting avenue for treatment of metastatic disease. In investigations of their anti-inflammatory properties, several NRs including PPARγ (67–69), PPARα (70), and ERα and ERβ (71–73) have been shown to directly or indirectly inhibit CCL5 expression in various contexts. Although NR expression profiling has not been done on tumor-associated MSCs, the therapeutic targeting of these or other anti-inflammatory NRs might be helpful in disabling MSC–cancer cell communication that contributes to tumor growth and metastasis.

Angiogenesis

Neovascularization is required to provide tumors with essential nutrients, oxygen, and removal of metabolic waste.

Endogenous inhibitors of angiogenesis have been shown to impair tumor growth, and NR ligands may serve as pharmacologic means to retard the angiogenic process. Indeed, agonists for VDR have been shown to inhibit tumor-induced angiogenesis in multiple sites including the colon (74), lung (75), prostate (76), and skin (77). Interestingly, VDR agonists induce apoptosis and cell-cycle arrest in tumor-derived endothelial cells (TDEC), yet these effects are not observed in endothelial cells isolated from normal tissues or from Matrigel plugs (78). These differential antiproliferative effects are appealing from a therapeutic standpoint and may be explained in part by epigenetic silencing of the vitamin D–degrading enzyme CYP24A1 in TDECs (79). Similarly, PPARα activation inhibits tumor angiogenesis in a cancer cell–nonautonomous manner by suppressing endothelial cell proliferation and VEGF production and by increasing expression of antiangiogenic TSP-1 and endostatin (80). Likewise, inhibitors of NOX1, an enzyme which generates ROS, have been shown to block tumor angiogenesis in a PPARα-dependent manner (81). PPARγ activation has also been shown to oppose endothelial cell proliferation and inhibit angiogenesis in multiple cancer types both via cancer cell–autonomous functions, such as promoting cell-cycle arrest, differentiation, and apoptosis, and via cancer cell–nonautonomous functions, including inhibition of the angiogenesis-promoting factors COX-2, VEGF, and basic fibroblast growth factor (82). These findings in the context of tumor angiogenesis are particularly interesting, given that both PPARα and PPARγ have an established proangiogenic function in cardiovascular

disease and diabetes (83), highlighting the context dependence of NR ligands and their physiologic outcomes.

Ligands for the glucocorticoid receptor (GR) have also been shown to inhibit tumor angiogenesis and tumor growth *in vivo*, both by decreasing VEGF and IL-8 production by tumor cells (84), leading to decreased microvessel density *in vivo*, and by blocking tube-like structure formation by vascular endothelial cells (85). These findings led in part to the development of a phase II clinical trial of combined treatment with the GR ligand dexamethasone and the VDR ligand calcitriol for castration-resistant prostate cancer (86), as antiangiogenic agents had previously yielded some of the most promising results for these patients with otherwise limited treatment options (87). Although the trial failed to produce a clinical response, alterations to therapeutic delivery, including the use of liposomal glucocorticoids (88), are currently under investigation and have yielded some promising results. Collectively, these findings point to NRs and their ligands as context-dependent antiangiogenic agents which may be beneficial in inhibiting tumor-associated neovascularization.

Inflammation and Immune Surveillance

Infiltrating cells of the immune system serve both tumor-antagonizing and tumor-promoting roles in the tumor microenvironment. Targeting NRs may be of value in both the activation of tumor cell–killing responses and inhibition of tumor-promoting inflammation. PPARγ, for example, has widespread anti-inflammatory roles in the immune system and has long been appreciated as a negative regulator of activation of monocytes (89), macrophages (90), and T lymphocytes (91). As these immune cell types play key roles in cancer-associated inflammation, PPARγ is regarded as a promising novel agent to target inflammatory pathways in epithelial malignancies (92). In addition to suppressing tumor-promoting inflammation, PPARγ may also serve to promote tumor-antagonizing immune function on the basis of its established function in noncancer contexts. Recent work has shown that PPARγ activation in dendritic cells coordinately regulates the CD1 cell-surface glycoproteins, which are responsible for the presentation of self- and foreign-modified lipids. Specifically, PPARγ activation leads to a reduction in CD1a levels and an increase in expression of CD1d, which in turn promotes the selective induction of invariant natural killer T (iNKT) cell expansion (93). These IFNγ-producing iNKT cells have been shown to promote tumor antigen–specific cytotoxic T-cell responses (94), although a direct connection between PPARγ activation and iNKT cell–mediated antitumor toxicity has not been shown.

Another NR, RA-related orphan receptor γt (RORγt), has been shown to play a critical role in the differentiation of NKp46^{+} lymphoid tissue-inducer (LTi) cells (95). LTi cells in turn produce IL-12, which induces expression of adhesion molecules within tumor-associated vessels and promotes the invasion of leukocytes into the tumor (96). RORγt also directs the differentiation of T helper 17 (T$_H$17)

cells, which display antitumorigenic activities in certain contexts (97). RA has been shown to reciprocally inhibit T$_H$17 cell differentiation and promote T regulatory (Treg) cell differentiation by inhibiting expression of RORγt (98). Treg cells have also been shown to suppress antitumor immunity (99). Therefore, compounds with the opposite effect, which is to promote RORγt expression and/or function, may also help to tip the immunologic balance toward antitumor immunity.

The broad anti-inflammatory functions of other NRs make them appealing therapeutic targets in the tumor microenvironment. VDR, for example, was identified by use of a systems biology approach as the best candidate master regulator of a genetic network that suppresses both inflammation and promotes tissue barrier function (100), leading to a predicted decrease in cancer susceptibility in skin. A connection between the anti-inflammatory function of VDR and decreased cancer risk has been shown in other tissues as well, such as colon (101) and prostate (102) tissue, and though VDR expression has been shown in a number of immune cell types, the precise cell types and mechanisms important for this VDR-mediated anti-inflammatory function remain to be determined. Taken together, the established roles of NRs in various cell types of the immune system point to several avenues for therapeutic potential in the tumor microenvironment.

Concluding Remarks

In this review, we highlight recent findings which reveal the therapeutic promise of NRs and their ligands in various cell types of importance to tumor initiation, progression, and metastasis. Beyond this simplified discussion, evidence exists for tumor-promoting roles of NRs in certain tissues or tumor types, suggesting that the therapeutic potential of any NR ligand is likely to be highly context specific. The interrelatedness of inflammation, epithelial integrity, and tumor susceptibility is increasingly appreciated, and evidence for this interrelationship stems in part from the increased risk for cancer development among patients with chronic inflammatory diseases. NRs have established beneficial roles in a number of these diseases which predispose to cancer, including diabetes, obesity, ulcerative colitis, hepatic fibrosis, and others (Fig. 2). This established benefit suggests that, in addition to the potential use of NR ligands in combinatorial cancer therapies, these drugs may be of great value as preventive measures against cancer development within high-risk populations.

Disclosure of Potential Conflicts of Interest

Acknowledgments

Grant Support

This work was supported, in part, by grants from Ipsen/Biomeasure, The Helmsley Charitable Trust, Howard Hughes Medical Institute, NIH (DK062434, DK090962) and National Health and Medical Research Council of Australia Project grant 512354. R. Evans is supported in part by a Stand Up to Cancer Dream Team Translational Cancer Research Grant, a Program of the Entertainment Industry Foundation (SU2C-AACR-DT0509). M.H. Sherman is supported by a NIH T32 training grant CA009370.

Received November 15, 2011; revised November 17, 2011; accepted November 22, 2011; published OnlineFirst December 1, 2011.

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Nuclear Receptors as Modulators of the Tumor Microenvironment

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