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## Molecular Pathways: Beta-adrenergic signaling in cancer

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### Abstract

$\beta$ -adrenergic signaling has been found to regulate multiple cellular processes that contribute to the initiation and progression of cancer, including inflammation, angiogenesis, apoptosis/anoikis, cell motility and trafficking, activation of tumor-associated viruses, DNA damage repair, cellular immune response, and epithelial-mesenchymal transition. In several experimental cancer models, activation of the sympathetic nervous system promotes the metastasis of solid epithelial tumors and the dissemination of hematopoietic malignancies via  $\beta$ -adrenoreceptor-mediated activation of PKA and EPAC signaling pathways. Within the tumor microenvironment,  $\beta$ -adrenergic receptors on tumor and stromal cells are activated by catecholamines from local sympathetic nerve fibers (norepinephrine) and circulating blood (epinephrine). Tumor-associated macrophages are emerging as key targets of  $\beta$ -adrenergic regulation in several cancer contexts. Sympathetic nervous system regulation of cancer cell biology and the tumor microenvironment has clarified the molecular basis for long-suspected relationships between stress and cancer progression and now suggest a highly leveraged target for therapeutic intervention. Epidemiologic studies have linked the use of  $\beta$ -blockers to reduced rates of progression for several solid tumors, and pre-clinical pharmacologic and biomarker studies are now laying the groundwork for translation of  $\beta$ -blockade as a novel adjuvant to existing therapeutic strategies in clinical oncology.

### Background

The  $\beta$ -adrenergic signaling pathway (Figure 1) mediates sympathetic nervous system (SNS)-induced fight-or-flight stress responses (1, 2). SNS neural fibers innervate virtually every major organ system of the body and can release micro-molar concentrations of the catecholamine neurotransmitter norepinephrine (NE) into target tissues in response to physiological, psychological, and environmental threats to homeostasis (1–3). Acute SNS activation also elevates catecholamine levels in circulating blood via the release of epinephrine (E) from chromaffin cells of the adrenal medulla and NE spill-over from vascular neuro-muscular junctions (1–3). Acute stress responses can elevate NE and E levels by >10-fold within seconds, but basal levels also fluctuate tonically over time in response to organismic and environmental conditions (1–3). In addition to central nervous system (CNS) control of general SNS neural outflow, local regulatory processes also influence SNS nerve fiber activity and catecholamine release and degradation. As a result, NE and E concentrations can differ substantially in solid tissues versus blood, as well as across different tissue environments at the same point in time (1–3).

The biological effects of NE and E are mediated by  $\alpha_1$ -,  $\alpha_2$ -, and  $\beta$ -adrenergic receptor families which show distinct patterns of tissue distribution and signal through distinct biochemical pathways (3, 4). The three subtypes of  $\beta$ -adrenergic receptor,  $\beta_1$ ,  $\beta_2$ , and  $\beta_3$ , are present at many sites of tumor growth and metastasis such as the brain, lung, liver, kidney, adrenal gland, breast, ovary, prostate, lymphoid tissues, bone marrow, and vasculature.  $\beta$ -

adrenergic signaling regulates the biological activity of several cancer-relevant cell types including epithelial cells, vascular myocytes and pericytes, adipocytes, fibroblasts, neural/glia cells, and most lymphoid and myeloid immune cells (3, 4). Ligation of  $\beta$ -receptors by NE and E activates the  $G_{\alpha s}$  guanine nucleotide-binding protein to stimulate adenylyl cyclase synthesis of cyclic 3'-5' adenosine monophosphate (cAMP). The resulting transient cAMP flux can regulate a diverse array of cellular processes via two major downstream effector systems (Figure 1).

One cAMP effector involves activation of protein kinase A (PKA), which subsequently phosphorylates serine or threonine residues on target proteins that bear PKA-receptive amino acid motifs (e.g., R-R-X-[S/T]-Y, where R = arginine, S = serine, T = threonine, X = any amino acid, Y = hydrophobic amino acid). PKA regulates a wide variety of cellular processes ranging from general metabolism and growth to cell-specific processes such as differentiation, morphology, motility, secretion, neurotransmission, and gene transcription. Gene expression effects are mediated by PKA-induced phosphorylation of transcription factors such as the cAMP Response Element Binding Protein/Activating Transcription Factor (CREB/ATF) family, which collectively engage approximately 20% of human genes (5, 6). PKA-induced transcriptional alterations often promote cell differentiation at the expense of proliferation, and coordinate transcriptome-wide responses to stress or homeostatic perturbation (5). PKA also activates the  $\beta$ -adrenergic receptor kinase (BARK), which subsequently induces  $\beta$ -arrestin to transiently desensitize further  $\beta$  receptor signaling and activate the Src/Ras/MAPK pathway (7). Recent work also shows that PKA can directly activate Src (A. Sood, unpublished data).

A second major cAMP effector involves the guanine nucleotide Exchange Protein activated by Adenylyl Cyclase (EPAC) (8). EPAC activates the Ras-like guanine triphosphatase Rap1A, which in turn stimulates downstream effectors B-Raf, MEK1/2, and ERK1/2. In addition to the well-known effects of the MAP kinase pathway on cell growth and proliferation, EPAC signaling accounts for many cAMP-induced effects on cell morphology, motility, and secretion dynamics. EPAC's effects can be distinguished from those of PKA through pharmacologic agonists and molecular manipulations (e.g., target-specific siRNA). Although some overlaps occur,  $\beta$ -adrenergic influences on inflammation, angiogenesis, and invasion appear to be mediated predominately by PKA induction of genes encoding cytokines and growth factors, whereas EPAC induces complementary but distinct effects on cell morphology and motility.

### **$\beta$ -adrenergic regulation of tumor biology**

Studies of  $\beta$ -adrenergic influence on tumor biology were motivated by epidemiologic observations associating stressful life circumstances with accelerated progression of incident cancers (9, 10) and studies linking the use of  $\beta$ -adrenergic antagonists (" $\beta$ -blockers") with reduced disease progression (11–15). Epidemiologic studies find the most consistent relationships between stressful conditions and progression of already-incident tumors, and relatively little data suggest that stress affects the initial incidence of cancer (9, 10). In vivo laboratory models also find the most consistent effects of experimentally imposed stress on xenograft and syngeneic tumor models (i.e., already initiated tumors) (16, 17), whereas effects on spontaneous incidence or primary tumor growth are less common (but do occur occasionally (18–21)). In mouse models of breast (22) and prostate carcinomas (16, 17), as well as malignant melanoma (23, 24) and leukemia (25, 26),  $\beta$ -adrenergic antagonists have been found to block stress-induced enhancement of tumor progression/metastasis without affecting primary tumor growth in vivo or tumor cell proliferation in vitro.  $\beta$ -adrenergic agonists have also been found accelerate in vivo tumor progression and metastasis in the absence of stress (16, 17, 22, 27).

Several cellular and molecular processes have been found to mediate  $\beta$ -adrenergic influences on tumor progression (Figure 1), including recruitment of macrophages into the primary tumor (22), increased expression of pro-inflammatory cytokines such as IL-6 and IL-8 by tumor cells (28–30) and immune cells (29), VEGF-mediated increases in angiogenesis (27, 31, 32), matrix metalloproteinase-related increases in tissue invasion (31, 33, 34), tumor cell mobilization and motility (17, 35, 36), FAK-mediated resistance to anoikis/apoptosis (37), BAD-mediated resistance to chemotherapy-induced apoptosis (16, 38).  $\beta$ -antagonists alone or in conjunction with non-steroidal anti-inflammatory agents (NSAIDs) have also been found to inhibit surgery-induced metastasis in animal models (24, 39, 40). Some evidence suggests that  $\beta$ -adrenergic signaling can also inhibit p53-mediated DNA repair (41), suppress cytotoxic T lymphocyte and NK cell responses (26), inhibit expression of Type I interferons (22, 42), upregulate the Her2 signaling pathway (43, 44), stimulate arachidonic acid signaling (45), activate gene expression by tumor-promoting viruses (9, 46), and upregulate the SNAI2 transcription factor regulating epithelial-mesenchymal transition (S. Cole, S. Lutgendorf, and A. Sood, unpublished data). Each of these dynamics may contribute to SNS-induced tumor progression in vivo, but has not yet been confirmed to do so in direct inhibitor studies of mediation. However, it is clear that SNS activation can regulate a wide range of cancer-related molecular pathways via both direct regulation of  $\beta$ -receptor-bearing tumor cells and regulation of other  $\beta$ -receptor-bearing cells present in the tumor microenvironment such as macrophages and vascular cells.

The SNS can potentially regulate tumor  $\beta$ -adrenergic signaling both via circulating NE/E and via local NE release from SNS nerve fibers. However, growing evidence suggests the later dynamic plays a dominant role. Analyses of catecholamine levels in human ovarian carcinomas document substantially higher NE levels in tumor tissue than in blood, and they find no detectable E in tumor tissue (as would be expected if blood were the primary source of tumor catecholamines) (47, 48). Intra-tumor NE levels also correlate with patient psychosocial risk factors and with tumor gene expression profiles, but blood levels of NE/E do not (47, 48). Both observations suggest a primary role for local nerve fiber-derived NE in driving  $\beta$ -adrenergic effects on tumor biology. Histological analyses of catecholaminergic fibers within human breast and ovarian carcinomas show extensive peri-vascular innervation and occasional radiation of nerve fibers into the tumor parenchyma (29)(E. Sloan, unpublished data). This pattern of SNS innervation is similar to that observed in other solid tissues (e.g., lymph nodes (49)) and provides a source of NE to directly regulate  $\beta$ -adrenergic receptors on both tumor cells and stromal cells (particularly tumor-associated macrophages (22)). Interestingly, data from the lymph node setting have shown that chronic stress can increase the density of SNS nerve fibers within parenchymal tissue (49). Activated macrophages may also synthesize catecholamines (50), but no evidence has yet shown this to occur within tumors. An additional pathway by which SNS activity may regulate cancer biology both within the primary tumor microenvironment and systemically at metastatic target sites involves  $\beta$ -adrenergic regulation of myelopoiesis (51–55) and its effects on monocyte/macrophage trafficking and gene expression (22, 52, 55). This implies that some  $\beta$ -adrenergic influences on tumor biology may originate outside the tumor, via SNS innervation of the bone marrow hematopoietic environment or catecholamine “conditioning” of trafficking monocytes that are ultimately recruited into the tumor microenvironment (22). Such dynamics would complicate the targeting of therapeutic interventions based on tumor tissue  $\beta$ -receptor expression, but they also imply that adjuvant therapy with  $\beta$ -antagonists may suppress systemic support for tumor progression.

## Clinical-Translational Advances

Because  $\beta$ -adrenergic signaling modulates tumor progression via multiple downstream molecular pathways,  $\beta$  antagonists may provide a highly-leveraged adjuvant therapy strategy

with pleiotropic impacts on the primary tumor, its surrounding microenvironment, and metastatic target sites. The biological appeal of this concept is enhanced by the widespread availability of safe, inexpensive, and well-understood  $\beta$  antagonists (4). However, several issues need to be resolved in order to establish the translational potential of  $\beta$ -blockers as adjuvant therapy for cancer.

The most pressing need involves direct assessment of  $\beta$  antagonists' clinical efficacy in randomized Phase II trials. Conflicting results from currently available non-randomized observational studies (11–15, 56) suggest that further observational studies are not likely to definitively establish  $\beta$ -blockers' clinical utility in cancer due to methodologic difficulties such as, 1.) confounding by indication (e.g., the primary historical indication for  $\beta$ -blockade, cardiovascular disease, shares common pathophysiologic drivers with cancer progression such as smoking, adiposity, and systemic inflammation), 2.) confounding with other pharmacologic exposures that may affect cancer progression (e.g., ACE inhibitors), 3.) absence of information on influential risk factors and treatment parameters (e.g., cardiovascular datasets provide limited information on cancer progression/mortality risk factors, and cancer-related datasets provide limited measures of  $\beta$ -blocker agents/ utilization), and, 4.) time- and practice pattern-related confounding of cancer survival trends with  $\beta$ -blocker utilization trends (particularly for non-selective  $\beta$ -antagonists which are most likely to be efficacious as outlined below). Randomized controlled trials provide the only certain way to overcome such biases and definitively assess  $\beta$ -antagonists' protective effects on clinical cancer progression. The availability of pre-clinical data and approved, safe, and inexpensive  $\beta$ -antagonists with well-understood pharmacology and minimal side-effects provide a favorable risk/benefit profile for initial Phase II proof-of-concept trials in clinical oncology.

Clinical trial initiation will require selection of optimal disease settings and treatment regimens for assessing clinical impact. Preclinical laboratory models and human pharmaco-epidemiologic studies both suggest that  $\beta$ -antagonists are likely to be most effective in inhibiting the micro-metastatic spread of early-stage tumors, as opposed to chemoprevention of new tumors or reduction of advanced tumor burdens. As such, it makes sense to target tumor types such as breast or prostate cancer that are routinely detected at early stage, metastasize via inflammatory and circulatory mechanisms already linked to  $\beta$ -adrenergic signaling, and are sufficiently prevalent to provide high-power detection of group differences amidst the low progression/recurrence rates characteristic of early stage disease. In the context of breast cancer, some epidemiologic data suggest that  $\beta$ -antagonists may be particularly valuable in the context of ER-/PR-/Her2- “triple negative breast cancer” (TNBC) (13). Initial trials should also target disease settings such as ovarian carcinoma and malignant melanoma for which extensive pre-clinical or pharmaco-epidemiologic data already exist and suggest a significant therapeutic potential.

Optimal  $\beta$ -antagonist regimens also need to be defined, including the specific agent, the timing of its initiation, and the duration of treatment. Pharmacologic dissection of pre-clinical models of ovarian, breast, and prostate cancer find SNS effects to be mediated predominately by  $\beta_2$ - or  $\beta_3$ -adrenergic receptors (16, 19, 27, 55). Non-selective  $\beta$ -antagonists such as Propranolol and Nadolol have been highly active in these model systems, but the more commonly prescribed  $\beta_1$ -selective agents such as Atenolol generally failed to inhibit SNS effects on tumor progression. Similar effects have been observed in pharmaco-epidemiologic analyses of breast cancer, with non-selective  $\beta$ -antagonists showing comparable (13) or greater protective effects than  $\beta_1$ -selective agents (12). Given these observations, the use of non-selective antagonists such as Propranolol would provide the broadest biological leverage and minimize the risk of missing an active  $\beta$ -receptor target. CNS adrenergic receptors appear to play a role in some protective effects of  $\beta$ -antagonists,

suggesting that CNS-penetrant agents such as Propranolol may be preferred over agents that do not cross the blood-brain-barrier such as Nadolol. Experimental data showing that  $\beta$ -antagonist inhibition of surgery-induced metastasis (24, 39, 40) suggest initiation prior to surgery (i.e., neo-adjuvant) and perhaps in combination with an NSAID. The duration of  $\beta$ -blockade required to reduce tumor progression/recurrence rates has not been determined, but long-term  $\beta$ -blockade has routinely been used in cardiology and would seem to provide an appropriate starting point in oncology.

$\beta$ -blocker treatment could potentially be targeted based on tumor characteristics such as the expression of  $\beta$ -receptors (57) or their downstream target genes (48), or based on patient characteristics such as stress or anxiety levels (9, 58, 59). However, there is currently no evidence that any patient- or tumor-level characteristics affect  $\beta$ -blocker efficacy in clinical oncology. As such, initial RCTs should target the general disease settings in which  $\beta$ -blockade is likely to be most effective (as outlined above) and collect additional patient- and tumor-specific data to support responder analyses identifying predictive biomarkers of treatment efficacy. There are several reasons why tumor  $\beta$ -receptor expression might not provide an accurate predictive biomarker, including the fact that receptor expression does not assess the amount of SNS NE/E ligand impinging upon the receptor and potential adrenergic effects at extra-tumoral sites such as metastatic target tissues or the bone marrow hematopoietic generation of subsequently infiltrating macrophages and lymphocytes (22, 60).

Although a variety of translational parameters remain to be optimized, a growing body of pre-clinical and pharmaco-epidemiologic data suggest that  $\beta$ -adrenergic antagonists hold considerable promise for inhibiting the pleiotropic effects of SNS activation on tumor progression and metastasis. Over the next few years, we can expect further data expanding the range of tumor types examined, identifying additional mechanisms of  $\beta$ -adrenergic effects on tumor progression, and initial RCTs assessing the efficacy of  $\beta$ -blockade as an adjuvant therapy in clinical oncology.

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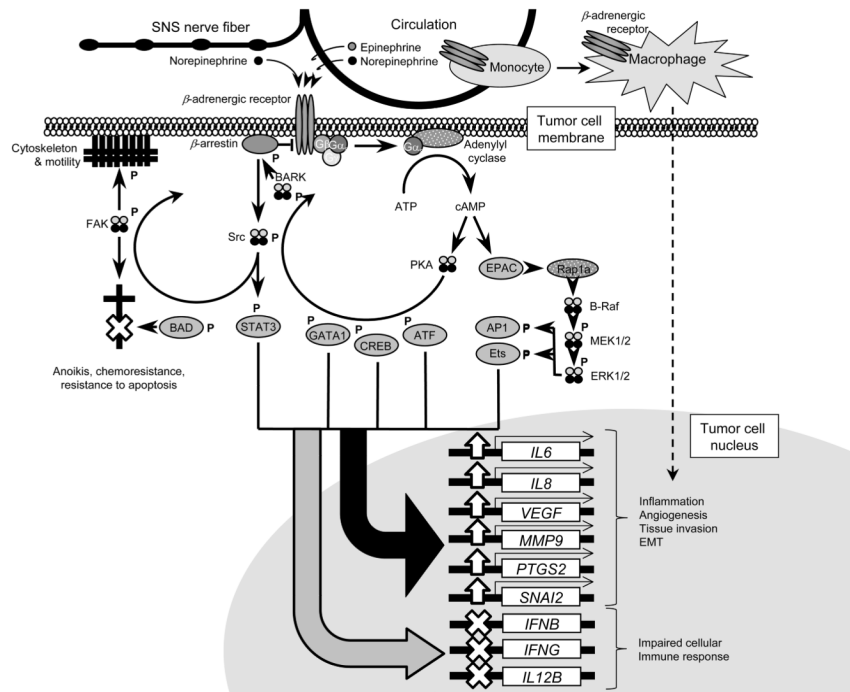
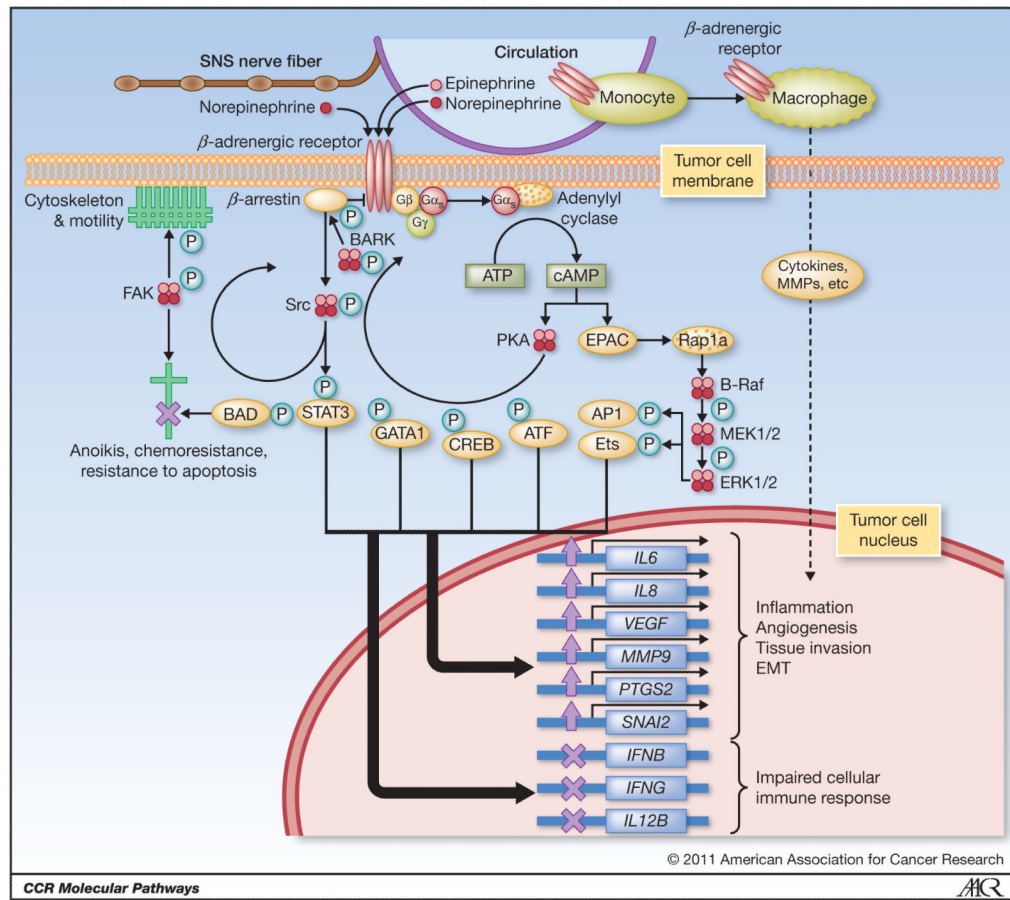
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**Figure 1. The  $\beta$ -adrenergic signaling pathway in cancer**

Sympathetic nervous system (SNS) fight-or-flight stress responses deliver epinephrine (E) and norepinephrine (NE) into the tumor microenvironment via circulating blood and NE release from local sympathetic nerve fibers. Both catecholamines bind to  $\beta$ -adrenergic receptors, resulting in G $\alpha$ s-mediated activation of adenylyl cyclase, and subsequent conversion of adenosine triphosphate (ATP) into cyclic 3'-5' adenosine monophosphate (cAMP). Transient flux of interacellular cAMP activates two major biochemical effector systems. (1) cAMP activates protein kinase A (PKA) to phosphorylate multiple target proteins including transcription factors of the CREB/ATF and GATA families, as well as the  $\beta$ -adrenergic receptor kinase (BARK). BARK recruitment of  $\beta$ -arrestin inhibits  $\beta$ -adrenergic receptor signaling and activates Src kinase, resulting in activation of transcription factors such as STAT3 and downstream kinases such as focal adhesion kinase (FAK). FAK activation modulates cell trafficking and motility via cytoskeletal dynamics, as well as cellular resistance to apoptosis (e.g., anoikis). PKA-dependent activation of Bcl-2 family member BAD can also render cancer cells resistant to chemotherapy-induced apoptosis. (2) In the second major effector pathway, cAMP activation of the Exchange Protein activated by Adenylyl Cyclase (EPAC) leads to Rap1A-mediated activation of the B-Raf/MAP kinase signaling pathway and downstream effects on diverse cellular processes including gene transcription mediated by AP-1 and Ets family transcription factors. The general pattern of transcriptional responses induced by  $\beta$ -adrenergic signaling includes up-regulated expression of metastasis-associated genes involved in inflammation, angiogenesis, tissue invasion, and epithelial-mesenchymal transition, and down-regulated expression of genes facilitating anti-tumor immune responses. In addition to direct effects on  $\beta$ -receptor-bearing tumor cells, SNS activation also modulates cancer biology by regulating the bone marrow generation and tumor recruitment and transcriptional activation of  $\beta$ -receptor-bearing monocyte/macrophages, as well as the growth and differentiation of vascular endothelial cells and pericytes.  $\beta$ -adrenergic effects on stromal cells in the tumor microenvironment generally synergize with direct effects on tumor cells in promoting cancer survival, growth, and metastatic dissemination.