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Beta-adrenergic signaling in the development and progression of pulmonary and pancreatic adenocarcinoma

Hildegard M. Schuller¹ and Hussein A. N. Al-Wadei^{1,2}

¹Experimental Oncology Laboratory, Department of Biomedical & Diagnostic Sciences, College of Veterinary Medicine, University of Tennessee, Knoxville, TN, USA

²Sana'a University, Sana'a, Yemen.

Abstract

Small airway epithelial cells from, which most pulmonary adenocarcinomas (PACs) derive, and pancreatic duct epithelia, from which pancreatic ductal adenocarcinomas (PDACs) originate, share the ability to synthesize and release bicarbonate. This activity is stimulated in both cell types by the $\alpha 7$ nicotinic acetylcholine receptor ($\alpha 7$ nAChR)-mediated release of noradrenaline and adrenaline, which in turn activate β -adrenergic receptor (β -AR) signaling, leading to the cAMP-dependent release of bicarbonate. The same signaling pathway also stimulates a complex network of intracellular signaling cascades which regulate the proliferation, migration, angiogenesis and apoptosis of PAC and PDAC cells. The amino acid neurotransmitter γ -aminobutyric acid (GABA) serves as the physiological inhibitor of this cancer stimulating network by blocking the activation of adenylyl cyclase. This review summarizes experimental, epidemiological and clinical data that have identified risk factors for PAC and PDAC such as smoking, alcoholism, chronic non neoplastic diseases and their treatments as well as psychological stress and analyzes how these factors increase the cancer-stimulating effects of this regulatory cascade in PAC and PDAC. This analysis identifies the careful maintenance of balanced levels in stimulatory stress neurotransmitters and inhibitory GABA as a key factor for the prevention of PDAC and suggests the marker-guided use of beta-blockers, GABA or GABA-B receptor agonists as well as psychotherapeutic or pharmacological stress reduction as important tools that may render currently ineffective cancer intervention of PAC and PDAC more successful.

Introduction

Beta-adrenergic receptors (β -ARs) and their signal transduction pathways are integral components of the sympathetic branch of the autonomic nervous system and mediate the biological effects of the catecholamine neurotransmitters noradrenaline and adrenaline. The regulatory role of beta-adrenergic signaling as it relates to cardiovascular disease, asthma and responses to psychological stress has been extensively investigated. However, relatively little is known about the contribution of beta-adrenergic signaling to the development and progression of cancer.

Pulmonary adenocarcinoma (PAC) and pancreatic ductal adenocarcinoma (PDAC) are among the most deadly forms of human cancer with 5-year survivals at or below 5% (1, 2). Both cancers are highly resistant to conventional chemo-and radiation therapy and the introduction of targeted agents that block individual cellular pathways has failed to add

significant survival benefits to either disease (1, 2). Smoking is a documented risk factor for both cancers and the tobacco-specific, nicotine-derived nitrosamine, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) induces PAC in rats, mice and Syrian golden hamsters (3, 4) and PDAC in rats and hamsters (5, 6). In addition to such direct carcinogenic effects of chemical carcinogens contained in tobacco products, nicotinic acetylcholine receptors (nAChRs) in the adrenal gland and sympathetic nervous system stimulate the release of the catecholamine neurotransmitters noradrenaline and adrenaline into the systemic circulation upon exposure to nicotine or NNK. In turn, these physiological β -AR agonists activate multiple signal transduction pathways in PAC and PDAC cells that stimulate cancer growth, metastasis and angiogenesis while inhibiting apoptosis (7).

Both, PAC and PDAC, frequently express activating point mutations in k-ras and inactivating mutations in the tumor suppressor gene p53 (8, 9). Discoveries that the formation of these mutations in animal models of cancer is associated with DNA adducts formed by interaction of NNK metabolites with DNA (10) have provided strong support for the somatic mutation theory, the prevailing paradigm in cancer research for over 50 years (11). However, recent studies have shown that neither the transfection of normal human airway epithelial cells with individual mutations in k-ras, p53 or the epidermal growth factor receptor (EGFR) nor the simultaneous expression of these mutations transformed the normal cells into cancer cells that had the ability to grow in nude mouse xenografts, suggesting that the somatic mutation theory has been overemphasized (12).

The arachidonic acid (AA) metabolizing enzyme cyclooxygenase 2 (COX-2), the epidermal growth factor receptor (EGFR), as well as the activated (phosphorylated) forms of the extracellular signal regulating kinase (ERK), of the tyrosine kinase family Src and of the serine/threonine protein kinase B (AKT) are frequently overexpressed in PAC and PDAC. Inhibitors of COX-2, EGFR-specific tyrosine kinases, ERK, Src and AKT alone and in combination have therefore been introduced as “targeted” therapeutics for these cancers, unfortunately with very little success (1, 2).

As shown in Figure 1, small airway epithelia, from which most PACs arise, and pancreatic duct epithelia, from which PDAC originates, share the ability to produce bicarbonate (13). In the lungs, bicarbonate reduces mucous viscosity while bicarbonate produced in the pancreatic ducts neutralizes stomach acidity. In both types of epithelia, the synthesis and release of bicarbonate is regulated by the autonomic nervous system. In response to binding of the neurotransmitter acetylcholine or its precursor, choline, to the $\alpha 7$ nicotinic acetylcholine receptor ($\alpha 7$ nAChR), nerve endings of the sympathetic release the catecholamine neurotransmitters noradrenaline and adrenaline. Both catecholamines bind as agonists to β -ARs expressed in epithelia of the small airways and pancreatic ducts, respectively (14, 15). The resulting activation of the stimulatory G-protein G_{α_s} and its downstream effector, adenylyl cyclase, causes the formation of intracellular cAMP that triggers the release of bicarbonate (Figure 1).

Interestingly, beta-adrenergic signaling also regulates the proliferation of small airway epithelial cells (16, 17) and pancreatic duct epithelia (18, 19) as well as the proliferation, migration, angiogenesis and apoptosis of PAC (20-23) and PDAC (24, 25) derived from these cells (Figure 2). In addition, studies in animal models suggest important regulatory roles of this signaling cascade in the development and progression of both cancers (26-28). The current review summarizes these experimental findings and discusses their correlation with epidemiological and clinical data as well as their significance for the development of more effective intervention strategies for PAC and PDAC.

Beta-adrenergic signaling in pulmonary adenocarcinoma (PAC)

Experimental Data

Tobacco smoke is a mixture of numerous toxic and carcinogenic agents. Nicotine is thought to be primarily responsible for the addictive properties of tobacco products and is generally regarded as non-carcinogenic. However, in vitro studies in human small cell lung cancer (SCLC) cells and experimental investigations in a hamster model of SCLC suggest that nicotine causes SCLC when nicotinic acetylcholine receptors (nAChRs) are sensitized by pathological increases in intrapulmonary CO₂ (29-31) typically found in the lungs of patients with chronic obstructive pulmonary disease (COPD). In support of these experimental data, COPD significantly increases the risk for the development of SCLC in smokers (32).

The nitrosamine NNK is formed from nicotine by nitrosation during the processing of tobacco and in the mammalian organism. NNK is the most powerful carcinogenic agent identified in tobacco products. It causes PAC in rats, mice and hamsters (3, 4) and is therefore thought to cause PAC in smokers. The NNK-induced PACs in hamsters originate from small airway epithelial cells (4), the primary site of PAC origin in humans. On the other hand, PACs induced by NNK in rats and mice arise from alveolar type II cells (33), a less common type of PAC in humans. In analogy to human PAC of both phenotypes, the NNK-induced lung tumors in all three rodent species express activating point mutations in k-ras and inactivating mutations in p53 formed by the interaction of NNK metabolites with DNA (34, 35). In addition, these experimentally induced PACs also over-express COX-2 and activated effectors of the EGFR pathway (36-39).

Discoveries that NNK is both, an agonist for the $\alpha 7$ nAChR with higher affinity than nicotine (40), and an agonist for β -ARs with higher affinity than noradrenaline/adrenaline (20), were landmark findings that have inspired research on the potential involvement of neurotransmitters and their receptor-mediated signaling pathways in the development and progression of smoking-associated cancer.

The first reports on a regulatory role of β -ARs in PAC were published in 1989 (21) and 1995 (41) when it was shown that the synthetic selective beta-adrenergic agonist isoproterenol stimulated the proliferation of PAC cell lines NCI-H322 and NCI-H441 with features of small airway epithelial cells via cAMP-dependent signaling. PCR analysis confirmed the expression of $\beta 1$ and $\beta 2$ -ARs in both cell lines, with $\beta 1$ -ARs predominating (20). In vitro exposure of immortalized small airway epithelial cells or these PAC cells to NNK significantly induced cell proliferation by two cooperating mechanisms: 1) the direct activation of the cAMP-dependent regulatory pathway by binding of NNK to β -ARs (20) and 2) the indirect activation of the same pathway by binding of NNK to the $\alpha 7$ nAChR that caused the release of the catecholamines noradrenaline and adrenaline which then bound to β -ARs (17). Interestingly, it was also shown that chronic treatment of small airway epithelial cells with NNK upregulated the protein expression of the $\alpha 7$ nAChR while additionally sensitizing this receptor, resulting in a significantly enhanced catecholamine response (17). In accord with epidemiological findings that PAC is more common in women than men (42), estrogen cooperated with the NNK-activated β -AR pathway in small airway epithelial cells by increasing intracellular cAMP via non-genomic mechanisms (16). In addition, chronic estrogen upregulated the protein expression and sensitivity of the $\alpha 7$ nAChR in these cells, leading to enhanced release of catecholamines in response to agonist (17). In vitro studies further revealed that in addition to the classic cAMP-dependent signaling pathway via activated protein kinase A (PKA) and phosphorylation of the transcription factor CREB, the EGFR pathway and its effector, the ras/ERK cascade was transactivated in a PKA-dependent manner by NNK (20, 22). Moreover, the release of EGF itself is under β -AR

control (43). Phosphorylation of the Src tyrosine kinases (44) and of the serine/threonine protein kinase B, AKT (45) reported by several laboratories in NNK-exposed airway epithelial cells or PAC cell lines were therefore likely the result of EGFR transactivation or EGF release by beta-adrenergic signaling. Moreover, it has been shown that beta-adrenergic signaling in response to NNK treatment stimulated the release of arachidonic acid (AA) from PAC cells and that the resulting induction of DNA synthesis was partially inhibited by inhibitors of COX-2 or 5-lipoxygenase while the general beta-blocker propranolol completely blocked this response (20). These in vitro findings are in accord with the over-expression of phosphorylated Src, AKT as well as COX-2 and 5-LOX in human PAC tissues and functionally connect these seemingly unrelated cellular pathways with beta-adrenergic signaling governed by the α_7 nAChR as their upstream regulator (Figure 2).

The proliferation and migration of PAC cells in response to the synthetic β -AR agonist isoproterenol was completely abrogated by treatment of the cells with the neurotransmitter γ -aminobutyric acid (GABA). This effect was mediated by binding of GABA to the $G\alpha_i$ -coupled GABA-B receptor and the resulting suppression of adenylyl cyclase activation, thus confirming the key role of cAMP-dependent signaling in the β -adrenergic regulatory cascade of PAC cells (23).

Interestingly, the proliferation of PAC cells and small airway epithelial cells via activation of PKA/p-CREB/p-ERK was also significantly stimulated when intracellular cAMP levels were increased by non beta-adrenergic stimuli. It has thus been shown that exposure of these cells to the glucocorticoid dexamethasone (46), the pro-vitamin A, β -carotene (47), several retinoids (48) or estrogen (16, 17) each stimulated cell proliferation via induction of cAMP by non-genomic mechanisms. In addition, the phosphodiesterase inhibitors caffeine (49) and theophylline (50) which increase intracellular cAMP by inhibiting its enzymatic breakdown, both significantly induced cell proliferation.

Several animal experiments have confirmed the regulatory role of the beta-adrenergic cascade in PAC that was first suggested by in vitro data (above). Studies in a hamster model of NNK-induced small airway-derived PAC have shown significant tumor promoting effects when β -ARs were additionally activated by treatment of the animals with epinephrine whereas the beta-blocker propranolol significantly prevented NNK-induced PAC development (26). Moreover, NNK treated hamsters had significantly elevated levels of systemic noradrenaline and adrenaline and increased cAMP in blood cells and tumor tissues accompanied by upregulated protein expression of the α_7 nAChR, p-CREB and p-ERK in tumor tissues (27). These findings represent the in vivo correlate to the in vitro upregulation and sensitization of the α_7 nAChR and its downstream catecholamine production observed after chronic exposure of PAC cells or their cells of origin to NNK or nicotine in vitro (17). Further corroboration of these data came from investigations in mouse xenografts from human PAC cell lines NCI-H322 and NCI-H441. Treatment of the mice with nicotine in the drinking water significantly increased xenograft growth while elevating the levels of noradrenaline and adrenaline in serum and xenograft tissues (51). In accord with the increased catecholamine levels, cAMP was elevated in blood cells and xenograft tissues and the protein expression of the α_7 nAChR as well as the expression of the signaling proteins p-CREB, p-ERK, p-Src and p-AKT were all induced in xenograft tissues. Interestingly, all of these responses to nicotine were completely reversed in mice treated with GABA injections (51). These findings corroborated the postulated dependence of nicotine-induced PAC progression on the beta-adrenergic activation of cAMP signaling. In addition, these data suggest that the nicotine-induced upregulation of the α_7 nAChR was also a cAMP-dependent response. Interestingly, the nicotine-exposed mice also demonstrated an impaired GABA system as evidenced by suppression of the GABA synthesizing enzyme glutamate decarboxylase 65 (GAD65) accompanied by decreased GABA levels in serum and tumor

tissues (51). In light of the documented tumor suppressor function of GABA on PAC (23), nicotine-induced GABA suppression may thus significantly contribute to the prevalence of PAC in smokers.

The tumor promoting effects of non beta-adrenergic agents that increase cAMP levels observed in vitro (above) was also corroborated by animal experiments. It has thus been shown that chronic treatment with, with beta-carotene significantly increased the multiplicity (number of tumors per animal) and size of NNK-induced PAC in hamsters (52). The increased tumor burden was accompanied by increased levels of cAMP in the circulating blood cells and induction of p-CREB and p-ERK in the tumor tissue. Similarly, chronic treatment with the phosphodiesterase inhibitor theophylline or with green tea, that contained theophylline and caffeine, significantly promoted NNK-Induced PAC development in this species (53). These findings are contrasted sharply by data generated in mouse models of PAC that have shown no effects of beta-carotene (54) while green tea even had significant cancer preventive effects on NNK-induced PAC in rats and mice (55). These seeming discrepancies of data generated in hamsters versus mice and rats are the reflection of differences in cellular lineage of PAC among these species. As pointed out in the introduction, NNK-induced PAC in hamsters arises from small airway epithelia whereas NNK causes the development of PAC from alveolar type II cells in rats and mice. In turn, in vitro experiments with human PAC cell lines A549 and NCI-H358, which express phenotypic and functional characteristics of alveolar type II cells, revealed a lack of responsiveness to the β -AR agonist isoproterenol whereas the cAMP activator forskolin inhibited cell proliferation and p-ERK expression (56).

Responses to psychological stress are initiated by release of the stress neurotransmitters noradrenaline and adrenaline and the stress hormone cortisol into the systemic circulation following activation of the hypothalamo/pituitary/adrenal axis (57). In addition, chronic psychological stress suppresses GAD and GABA while impairing GABA-ergic networking via non-genomic effects of cortisol (58, 59). The resulting prevalence of β -AR-stimulating catecholamine neurotransmitters, accompanied by nongenomic increase in cortisol-induced cAMP and suppression of cAMP-inhibiting GABA should therefore have strong promoting effects on the development and progression of small airway-derived PAC. In support of this hypothesis, a recent experiment in mice carrying human xenografts from PAC cell lines NCI-H322 or NCI-H441 has shown a significant promotion of xenograft growth in animals that were exposed to social stress (60). Systemic and tumor levels of noradrenaline, adrenaline, cortisol and cAMP were also significantly elevated by stress. In addition, p-ERK and p-CREB were significantly induced in tumor tissue. By contrast, systemic levels of GABA and tumor levels of GAD and GABA were suppressed by stress. Interestingly, the protein expression of nAChRs containing the subunits $\alpha 3$, $\alpha 4$, $\alpha 5$ and $\alpha 7$ was over-expressed in xenograft tissues indicating that effectors of these receptors contributed to the observed cancer promoting effects of stress (60). Treatment of the mice with GABA in the drinking water completely reversed all of these responses to stress and reduced tumor growth significantly below base levels observed in mice not exposed to stress (60). These findings provide strong support to the hypothesis that psychological stress promotes PAC progression via beta-adrenergic signaling and emphasizes the central importance of cAMP in the observed responses, an interpretation in accord with similar findings in ovarian cancer (61). In addition to these direct effects of stress-induced beta-adrenergic signaling on lung cancer growth, indirect effects on the metastatic potential of cancer cells via catecholamine-induced impairment of the immune system have also been reported (62). Although the latter study was conducted with a rat breast cancer model, the reported inhibition of NK cell activity would non selectively enhance the metastatic potential of any type of cancer.

Epidemiological and clinical data

Smoking is the strongest known risk factor for all lung cancers, including PAC (63). However, among the four major histological types of lung cancer (listed in order of frequency: adenocarcinoma, squamous cell carcinoma, small cell lung carcinoma, squamous cell carcinoma, large cell carcinoma) PAC is the only cancer that develops in a significant number of individuals who have never been exposed to tobacco smoke. In addition, PAC is significantly more common in women than men and blacks have a higher incidence of PAC than other ethnic groups (42, 64). While the other histological types of lung cancer have declined in incidence with the reduction of active smokers in recent years, the number of PAC cases continues to rise, and PAC has become the most common lung cancer today (42, 65). Epidemiology thus suggests that factors unrelated to smoking exert a significant influence on PAC development and progression. For example, the prevalence of PAC in women may be associated with the cooperation of beta-adrenergic and estrogen signaling revealed by in vitro experiments (16, 17). On the other hand, the high incidence of PAC in blacks may be at least in part stress-related in light of the lower socio-economic status of a large proportion of this ethnic group. A significant tumor promoting effect of psychological stress on lung cancer in general is also supported by observations that lung cancer patients with high levels of stress have a higher mortality and less favorable clinical outcomes (66) and that comparison of stress levels in patients with cancer from various sites revealed particularly high levels of psychological distress in lung cancer patients (66).

Chronic obstructive pulmonary disease (COPD), chronic bronchitis, emphysema and asthma are documented risk factors for all histological types of lung cancer in smokers and non smokers (32, 67, 68). A recent study in Chinese women who never smoked reported asthma as a significant risk factor for adenocarcinoma (69). While the association of previous pulmonary disease with lung cancer has been mostly blamed on the increase in inflammatory mediators and changes in gene profiles, little attention has been given to the fact that the leading therapeutics for this disease family are agents that stimulate β -ARs directly (β 2-AR agonists and epinephrine inhalers are used as bronchodilators; numerous over the counter decongestants contain epinephrine or structurally related agents). In addition agents that increase intracellular cAMP levels and therefore have broncho-dilating and anti-inflammatory actions, are frequently prescribed to these patients either alone or in combination with β -AR agonists (general phosphodiesterase inhibitor theophylline, selective phosphodiesterase inhibitors). Moreover, corticosteroids are frequently prescribed because of their anti-inflammatory properties while in vitro studies with PAC cell lines and airway epithelial cells have shown that these agents increase intracellular cAMP via non-genomic mechanisms while additionally intensifying the cAMP response to β 2-AR agonists (46, 70). Since the majority of these chronic non-neoplastic pulmonary diseases are caused by smoking and always precede a diagnosis of lung cancer, it has to be considered that many of these patients have precancerous or microscopic neoplastic lesions in their lungs whose development is then greatly promoted by the broncho-dilating and anti-inflammatory therapeutics they use. In fact clinical trials with the selective phosphodiesterase-4 inhibitor Roflumilast that was recently FDA approved for the treatment of COPD in the USA, have reported a disproportionably greater incidence of lung cancer and prostate cancer in the patients treated with Roflumilast than in the placebo group (71). The authors interpreted this finding as a possible “chance observation” arguing that the one-year observation period was too short for the induction of these cancers. However, the possibility of a cancer promoting effect on pre-existing precancerous lesions or tumors of microscopic size via increased cAMP signaling cannot be excluded in light of the fact that prostate cancer (72, 73) and the leading lung cancer PAC (7) are both stimulated by cAMP signaling.

The most notorious examples for therapeutic agents that underwent clinical testing for the prevention of lung cancer and turned out to increase lung cancer incidence and mortality

instead were beta-carotene and retinol. The carotene and retinol efficacy trial (CARET) was conducted to test the lung cancer preventive effects of beta-carotene and retinol in smokers and individuals exposed to asbestos (74). The trial had to be stopped after 4 years due to a significant increase in lung cancer incidence and mortality in both cohorts, with PAC representing the leading histological tumor type (75). The observed adverse effects of beta-carotene were similar to those reported in the alpha-tocopherol and beta-carotene cancer prevention study (76). While at the time no explanation for this adverse outcome was available, *in vitro* studies in PAC cell lines (47) and an experiment with NNK-induced PAC in hamsters (52) later revealed that both agents stimulate the growth and progression of PAC via non-genomic activation of cAMP signaling.

Several epidemiological studies have investigated the potential beneficial effects of anti-hypertensive agents on cancer risk and clinical outcomes with variable results (77-82). Some of these investigations included lung cancer cases, but found either no significant effect or only minor modulations. A common problem with such studies is the diversity of lung cancers and their antagonistic growth regulation. Experimental investigations have thus shown that β -AR agonists and cAMP stimulate small airway-derived PAC (discussed above) while identical agents inhibited the growth of small cell lung cancer cells (83, 84) and squamous cell carcinoma cells (85) while having no effect or growth inhibiting effects on PAC cells of alveolar type II cell phenotype (54, 56, 76, 86, 87). It is thus impossible to detect beneficial effects of any agent that inhibits β -ARs or cAMP signaling when looking at lung cancer in general, without discriminating between individual histological tumor types. However, the experimentally established significance of beta-adrenergic cAMP-dependent signaling in the regulation of small airway-derived PAC has been amply validated by the disastrous outcome of the CARET trial (74, 75). Additional support for this interpretation comes from epidemiological studies that have reported protective effects of wine drinking against lung cancer, particularly adenocarcinoma (88). It was thought that polyphenols with anti-oxidant and anti-inflammatory actions contained in wine were responsible for this effect. However, wine also contains significant levels of GABA (89) which has shown strong inhibiting effects on PAC growth and progression *in vitro* and in animal models by reducing cAMP signaling (see experimental data, above).

Beta-adrenergic signaling in pancreatic ductal adenocarcinoma (PDAC)

Experimental Data

First evidence for the involvement of beta-adrenergic signaling in the regulation of PDAC came from the *in vitro* observation that the two human PDAC cell lines Panc-1 and BXPC-3 synthesized and released arachidonic acid (AA), a function that was increased by binding of NNK to β 2-ARs and inhibited by the selective β 2-AR antagonist ICI118,551 while the selective β 1-AR antagonist atenolol had little effect (24). These findings were supported by radio-receptor binding assays and PCR analyses that confirmed the expression of β 1- and β 2-ARs in both cell lines, with β 2-ARs predominating. NNK also stimulated DNA synthesis and cell proliferation in both cell lines, a response inhibited by the β 2-AR blocker and partially inhibited by the COX inhibitor aspirin or the 5-lipoxygenase (5-LOX) inhibitor MK-886 (24). These findings are in accord with the regulation of AA release by β 2-ARs reported in cardiomyocytes (90) and suggest that eicosanoids formed by the COX and 5-LOX-mediated metabolism of AA contributed to the observed NNK-induced proliferation of PDAC cells. In analogy to studies in PAC cells, investigations in immortalized human pancreatic duct epithelial cells HPDE6-C7 additionally revealed the cAMP-dependent phosphorylation of CREB, ERK and EGFR-specific tyrosine kinases in response to β -AR agonists and showed that exposure of the cells to ethanol significantly enhanced these responses while inhibitors of cAMP formation or protein kinase A (PKA) activation significantly reduced these responses and cell proliferation (18, 19). Additional support for

the importance of cAMP signaling in the regulation of PDAC cell proliferation came from in vitro experiments that reported a significant stimulation of PDAC cell proliferation associated with the activation of PKA, CREB, ERK and EGFR-specific tyrosine kinases in response to beta-carotene or the synthetic cAMP stimulator forskolin (91). Furthermore, it was shown that β -AR-induced DNA synthesis and migration of PDAC cells or immortalized pancreatic duct epithelial cells was blocked by treatment of the cells with GABA that reduced the formation of cAMP. This effects was enhanced by transient over-expression of the $G\alpha_i$ -coupled GABA-B receptor and abolished by gene knockdown of this receptor (92). These data indicate that the observed reduction of cAMP in response to GABA treatment was caused by the $G\alpha_i$ -mediated inhibition of adenylyl cyclase, the rate-limiting enzyme in the formation of cAMP. Another laboratory corroborated and extended these findings by showing that ICI118,551 inhibited the proliferation and metastatic potential of PDCA cell lines Mia PaCa-2 and BXPC-3 and that these effects were accompanied by reductions in the activation of CREB, nuclear factor κ B, COX-2, metalloproteinase-2 and vascular endothelia growth factor (93). This research group also reported that norepinephrine-induced migration of PDAC cells was inhibited by the general β -AR antagonist propranolol (94) and that propranolol induced apoptosis in these cells (95). Interestingly, a recent in vitro study revealed that PDAC cell lines Panc-1 and BXPC-3 as well as immortalized pancreatic duct epithelial cells HPDE6-C7 synthesized and released the catecholamine neurotransmitters noradrenaline and adrenaline upon exposure to acetylcholine, nicotine, or NNK and that this activity was abolished by inhibition of the $\alpha 7$ nAChR by gene knockdown or the selective $\alpha 7$ nAChR antagonist α -bungarotoxin (96). Moreover, these experiments showed that nicotine induced cell proliferation and phosphorylation of CREB, ERK, Src and AKT in all three cell lines and that these responses were abrogated by the general beta-blocker propranolol (96). In light of these findings, nicotine-induced proliferation and migration of PDAC cells associated with secretion of osteopontin and activation of ERK and metalloproteinases as well as induction of VEGF that were initially interpreted as direct responses downstream of nAChRs (97, 98) were likely also caused by the indirect stimulation of these activities by the $\alpha 7$ nAChR-initiated release of norepinephrine and epinephrine, leading to the activation of β -AR signaling .

The in vivo relevance of the summarized in vitro findings is supported by observations that prenatal exposure of hamsters to NNK and ethanol causes a high incidence of PDAC accompanied by pancreatitis (6) and that postnatal treatment of the animals with the COX inhibitor ibuprofen or the 5-LOX inhibitor MK-886 prevented the development of PDAC and pancreatitis in this animal model by 50 and 30%, respectively (99) while the beta-blocker propranolol completely prevented the development of PDAC (28). The experimentally induced PDACs in this animal model overexpressed $\alpha 7$ nAChR protein as well as p-CREB , p-ERK, EGF and VEGF. By contrast, GAD65, GAD67 and GABA were suppressed in tumor tissue. Treatment of the hamsters with propranolol reversed all of these responses (27, 28). The selective COX-2 inhibitor etodolac also demonstrated significant cancer preventive effects in a hamster model of PDAC induced by the synthetic nitrosamine N-nitrosobis(2-oxopropyl)amine (100). On the other hand, ethanol, which intensifies β -AR signaling in vitro by increasing cAMP (see, above) had significant tumor promoting effects in a mouse model of 7,12-dimethylbenzanthracene-induced PDAC (101). Collectively, these in vivo data are in accord with the PDAC regulatory pathway that illustrates members of the AA cascade as a downstream effectors of beta-adrenergic signaling (Figure 2).

Investigations in nude mice carrying xenografts of the PDAC cell line Panc-1 have shown that treatment of the animals with nicotine had strong tumor promoting effects that were accompanied by systemic increases in noradrenaline, adrenaline and cAMP while GABA levels were reduced (102). In addition, nicotine induced the expression of p-CREB and p-ERK while reducing GAD expression in xenograft tissues. Treatment of the mice with

GABA completely abolished the stimulating effects of nicotine on tumor growth while also significantly reducing xenograft growth in mice not exposed to nicotine. In addition, GABA inhibited the induction of cAMP, upregulation of p-CREB and p-ERK and prevented the suppression of GAD (102). The observed strong inhibitory actions of GABA in these experiments emphasize the key role of beta-adrenergic cAMP signaling (Figure 2) in the regulation of smoking-associated PDAC. Moreover, these findings are in accord with the well documented nicotine-induced release of stress neurotransmitters from peripheral postganglionic sympathetic nerves and the adrenal medulla (103). The more recent in vitro findings that PDAC cells and pancreatic duct epithelia produce levels of noradrenaline and adrenaline that are detectable in the absence of nicotine and enhanced by nicotine exposure (96) additionally explain why GABA suppressed tumor growth also in mice not treated with nicotine. Investigations in rats initially appeared to contradict the PDAC inhibiting effects of GABA as they reported the induction of exocrine pancreatic tumors in rats by the GABA analogue Gabapentin (104). However, the induced pancreatic tumors were derived from pancreatic acinar cells and not pancreatic duct epithelial cells (105). In addition, more recent publications revealed that Gabapentin does not act via the GABA-B- receptor (106) that was found to mediate the inhibitory actions of GABA in PDAC cells (92), and even activates the noradrenergic system (107). Another seemingly contradictory finding was the observation that GABA selectively stimulated the growth of PDAC cell lines that over-expressed the GABA-A receptor pi subunit (108). However, GABA-A receptors are ion channels that do not inhibit adenylyl cyclase activation as the $G\alpha_i$ -coupled GABA-B receptor and over-expression of their pi subunit may therefore have caused a prevalence of excitatory responses to GABA.

Beta-adrenergic signaling plays an important role in responses to psychological stress that are triggered by the release of the stress neurotransmitter noradrenaline and adrenaline and the stress hormone cortisol (57). Accordingly, psychological stress may have promoting effects on PDAC. This hypothesis was recently tested in mouse xenografts from PDAC cell lines Panc-1 and BXP-3. Mice exposed to chronic social stress had significantly elevated levels of noradrenaline, adrenaline, cortisol and VEGF in serum and xenograft tissues. In addition, cAMP, p-CREB, p-ERK, p-Src, p-AKT, VEGF as well as protein expression of nAChR subunits $\alpha 3$, $\alpha 4$, $\alpha 5$, $\alpha 6$, and $\alpha 7$ were induced in xenograft tissues, while the expression of GAD and GABA levels were suppressed and expression of $\beta 1$ - and $\beta 2$ -ARs remained unchanged. These reactions to stress were accompanied by a significant promotion of tumor growth. The tumor promoting effects of stress as well as the upregulation of nAChRs, signaling proteins, cAMP and VEGF were completely blocked in animals treated with GABA (109). These findings provide first experimental evidence for significant cancer promoting effects of psychological stress on PDAC via beta-adrenergic, cAMP-dependent induction of multiple signaling pathways (Figure 3) and impairment of the GABA system and identify this hitherto unknown neuroendocrine regulation of PDAC as a novel target for cancer intervention. In addition, these data indicate that the clinical failure of chemotherapeutics for PDAC that were highly effective in preclinical tests may, at least in part, be due to the psychological stress of cancer patients that is lacking in the preclinical in vivo and in vitro test systems.

Epidemiological and clinical data

Smoking, diabetes mellitus and pancreatitis of any etiology, including alcoholism, are risk factors for pancreatic cancer (110, 111). The experimental findings that have identified the indirect activation of beta-adrenergic cAMP-dependent signaling in PAC cells by the nicotine -or NNK-induced release of noradrenaline and adrenaline in conjunction with direct stimulation of this signaling cascade by ligand-binding of NNK as an agonist to β -ARs provide mechanistic insights into mechanisms of smoking-associated PDAC development.

They also raise concern about potentially adverse effects on clinical outcomes of nicotine replacement therapy used by many cancer patients at the time of cancer diagnosis.

Diabetes mellitus is characterized by the destruction of pancreatic islet β -cells. However, in addition to providing insulin needed for the regulation of blood glucose levels, these cells are also a major source of pancreatic GABA production (112). In light of the strong PDAC inhibiting effects of GABA via reduction in cAMP-dependent signaling observed in the experimental studies (above), pancreatic GABA deficiency may therefore be an important factor that increases the risk of diabetic patients for the development of PDAC. Similarly, it has been shown that patients with pancreatitis have significantly reduced systemic GABA levels (113). Furthermore, the pain caused by chronic pancreatitis leads to increased sympathetic activity associated with increased levels of systemic noradrenaline (114). In light of the experimental findings summarized above, the resulting simultaneous hyperactivity of beta-adrenergic signaling and impaired inhibitory GABA signaling has to be considered a major driving force in the frequently observed development of PDAC in patients with preceding pancreatitis. In addition, corticosteroids are frequently used for the chronic management of pancreatitis (115). The experimentally identified non-genomic activation of cAMP signaling by these agents (46) may further intensify the responsiveness of PDAC cells and their cells of origin to beta-adrenergic stimulation.

To our knowledge, a potential protective effect of beta-blockers on PDAC development, progression, or clinical outcome has not been investigated to date. However, the routinely used therapeutics for the chronic management of cardiovascular disease aim to block the function of β 1-ARs. By contrast, the predominating β -AR that regulates PDAC and its cells of origin is the β 2-AR. In addition, chronic treatment with some beta-blockers has been shown to cause a reactive upregulation of β 2-ARs (116, 117) which may actually increase the risk for PDAC. Epidemiological studies for the assessment of PDAC risk and outcome in populations receiving chronic beta-blocker therapy for the management of cardiovascular disease are therefore unlikely to yield meaningful data.

Pancreatic cancer patients have the highest level of psychological stress of all investigated types of cancer (66) and cancer mortality is significantly increased by high levels of psychological stress (118). These findings support our experimental observations that psychological stress significantly promotes the growth and progression of PDAC via beta-adrenergic signaling activated by stress neurotransmitters (109).

Conclusions and Future Directions

The experimental data summarized in this review clearly show that multiple intracellular pathways that regulate the proliferation, migration, angiogenesis and apoptosis of cancer cells are regulated in PAC and PDAC cells and their cells of origin by β -ARs. The stimulation of noradrenaline and adrenaline production by the α 7nAChR and of GABA by the α 4 β 2nAChR adds the cholinergic system as upstream regulator to this signaling cascade (Figure 2). However, this complex network of cancer stimulating pathways has three distinct levels at which the entire network can be effectively interrupted: α 7nAChRs, β -ARs and adenylyl cyclase/cAMP. Investigations in mouse models of lung cancer have shown that treatment of the animals with cobra toxin that blocks the α 7nAChR significantly reduced cancer promotion (119). However, attempts at blocking the α 7nAChR would have severe side-effects in human patients due to the vital functions of this receptor in the nervous system, immune system and inflammatory responses (7). Cancer intervention of PAC and PDAC at the level of β -ARs or adenylylcyclase/cAMP provide realistic and hitherto unexplored opportunities. Beta-blockers have been safely used for the management of cardiovascular disease for decades. The prescription of these agents for off label cancer

intervention therefore does not require lengthy clinical trials. However, the long-term use of some of these agents can lead to the reactive upregulation of β -ARs, particularly the β 2-AR (116, 117) with potentially deleterious effects on cancer of the pancreas, breast, colon, and prostate, all of which express predominantly β 2-ARs. Treatment with beta-blockers should therefore be short-term (e.g. after surgical resection or at start of chemo-radiation therapy to improve clinical outcomes and prevent metastasis and relapse) and the potential upregulation of β -ARs should be carefully monitored in circulating lymphocytes. In addition, the decision to treat with beta-blockers should be based on clinical data that identify elevated systemic levels of noradrenaline, adrenaline, and/or cAMP. This is particularly important in the case of lung cancer, where the heterogeneity of this cancer family presents with antagonistic growth regulating pathways (7). On the other hand, the pharmacological boosting of the adenylyl cyclase inhibiting GABA system by treatment with GABA or selective GABA-B-receptor agonists such as Baclofen, appears to be well suited for long-term cancer intervention, provided such therapy is based on the detection of elevated systemic levels of cAMP and/or deficiency in systemic GABA and these substrates are regularly monitored during therapy. As the experimental data show, systemic cAMP can be assessed in the cellular fraction of blood while systemic GABA levels can be determined in serum samples. In either case, the systemic levels correlated well with the levels of these substrates in tumor tissue (27, 51, 60, 109). GABA is synthesized by plants as a defense against parasites and stress, such as adverse temperatures (120). It is enriched in germinated brown rice (121) and red wine (89), the technology for the production of GABA enriched grains (122) and dairy products (123) is available, and GABA has been safely used as a dietary supplement for many years because of its muscle relaxing and anxiolytic effects. Cancer intervention with GABA could therefore be achieved by a nutritional approach. Selective GABA-B receptor agonists such as Baclofen are approved prescription drugs for the treatment of muscle spasms and pain associated with spinal injury or degeneration and their off-label prescription for cancer intervention would be entirely legal.

It has been suggested in 2008 that the most common human cancers are significantly promoted by a lack of balance in stimulatory and inhibitory autonomic neurotransmission and its effectors (124). Experimental data generated since have expanded this concept to include a significant role in cancer etiology and therapeutic outcomes. Epidemiological investigations aimed at proving or disproving this concept by looking at the long-term effects on cancer risk and clinical outcomes of antihypertensive agents, beta-blockers or other agents that inhibit individual components of the regulatory cascade for PAC and PDCA (Figure 2) are severely compromised by the numerous factors that can influence the cascade. In fact, such studies will only be able to discover with statistical significance the “tip of the iceberg”. In light of this, a recent report that the long-term use of beta-blockers improved clinical outcomes in breast cancer patients (125) has to be considered highly significant as the beneficial effects must have been truly substantial to become detectable by epidemiological tools. Reports on risk factors for PAC and PDAC, including not only smoking but also preceding non-neoplastic diseases and their treatments as well as failed cancer prevention trials, are just as informative or even more so, provided the question is considered: what effects do these factors have on the beta-adrenergic regulatory cascade?

In light of the central role of beta-adrenergic signaling in stress responses, the potentially deleterious effects of psychological stress on the development, progression and clinical outcomes of PAC and PDCA cannot be over-emphasized. The significant activation of multiple β -AR-dependent cancer stimulating pathways by psychological stress reported in xenograft models of PAC (60) and PDAC (109) are complemented by similar findings in ovarian cancer (61). Collectively, these data should motivate every clinical oncologist to provide his/her patients with psychotherapeutic and/or pharmacological management of stress to improve clinical outcomes of cancer therapy.

Hundred thousands of people globally succumb every year to cancer. Cancer research has made great strides in improving 5-year survivals of patients with breast cancer, colon cancer and prostate cancer, mostly thanks to improved technologies for early detection. But there is very little information on actual cures, such as 20-30 year survivals. Furthermore, clinical outcomes for patients with PAC or PDAC have not improved at all. These cancers are typically detected at an advanced stage, and despite of intense research, 5-year survivals are at or below 5 %. The stubborn adherence of the scientific community to outdated concepts such as the somatic mutation theory, which has prompted numerous efforts to block individual molecular targets, with no success, contributes to the catastrophic prognosis of these cancers. Extensive research of isolated cancer cells separated from their natural micro- and macro-environment has created additional confusion. Like every other mammalian cell, cancer cells are not living in an isolated vacuum but are part of the highly complex mammalian organism whose responses to internal changes and external challenges are carefully orchestrated by the autonomic nervous system. This system becomes overwhelmed when incoming signals mimic physiologic neurotransmitters (nicotine and NNK), psychological stress shifts the balance towards cancer-stimulating β -adrenergic signaling, chronic disease and/or their treatments or misguided attempts at cancer prevention enhance the cancer stimulating arm of the regulatory cascade while in some cases additionally weakening the inhibitory GABA system. While the strict avoidance of exposure to tobacco products continues to be the most effective method of cancer prevention, there is no such thing as a single agent that prevents all cancers. In fact, such attempts can do more harm than good because of the diversity of regulatory pathways expressed in different types of cancer, a lesson we have learned the hard way from the CARET (74, 75) and alpha-tocopherol (76) trials. The early diagnosis of pathological levels in systemic stress neurotransmitters, cAMP and GABA can be used in a targeted manner to identify individuals at increased risk for the development of cAMP- driven cancers and appropriate measures to restore the balance can then be taken. We have to finally accept that it is just as important for our long-term survival to maintain balanced levels of stimulatory and inhibitory neurotransmitters as it is to maintain balanced levels of good and bad cholesterol or balanced levels of insulin and glucose. In fact, the successful long-term management of these incurable non-neoplastic diseases is the perfect example for a therapeutic approach that utilizes continued careful monitoring to restore physiological balance.

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Figure 1. Physiological role of beta-adrenergic signaling in the regulation of cAMP-dependent bicarbonate secretion by small airway epithelial cells and pancreatic duct epithelial cells.

Figure 2.

Cooperative regulation by the α_7 nAChR and β -ARs of a complex network of cancer-stimulating pathways in PAC and PDAC and the inhibitory potentials of beta-blockers and GABA-ergic agents.