SPANDIDOS PUBLICATIONS

BIOMEDICAL REPORTS 4: 515-518, 2016

Nicotinic acetylcholine receptors and cancer (Review)

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Received November 11, 2015; Accepted March 1, 2016

DOI: 10.3892/br.2016.625

Abstract. Nicotine, the primary addictive constituent of cigarettes, is believed to contribute to cancer promotion and progression through the activation of nicotinic acetylcholine receptors (nAChRs), which are membrane ligand-gated cation channels. nAChRs activation can be triggered by the neurotransmitter Ach, or certain other biological compounds, such as nicotine. In recent years, genome-wide association studies have indicated that allelic variation in the α5-α3-β4 nAChR cluster on chromosome 15q24-15q25.1 is associated with lung cancer risk. The role of nAChRs in other types of cancer has also been reported. The present review highlights the role of nAChRs in types of human cancer.

Contents

1. Introduction

Acetylcholine receptors (AChRs), similar to a number of other ligand-activated neurotransmitter receptors in neuronal system, consist of 2 subtypes: Metabotropic muscarinic receptors and ionotropic nicotinic receptors (1). These 2 subtypes can be activated by the endogenous neurotransmitter ACh (1). The first subtype, the metabotropic muscarinic receptors, is G protein-coupled seven-transmembrane proteins, which directly alter the cellular homeostasis of phospholipase C, inositol-3-phosphate, cyclic adenosine monophosphate and free calcium. Activation of metabotropic AChRs is relatively slow (from msec to sec). The other AChR subtype is the fast ionotropic cationic nicotinic AChRs (nAChRs). These ion channels are sensitive to activation by acetylcholine and nicotine, and their activation is extremely fast (msec to sub-msec) (1). nAChRs consist of 5 subunits, comprising 10 α subunits (from α1 to α10), 4 β subunits (from β1 to β4), 1 δ, and 1 ε or γ subunit. The receptors can form homo- or hetero-pentamers, and enclose a central ion channel. The nAChR subunit composition also has a role in regulating the function of nAChRs (1-3). All the nAChRs show permeability to various cations, such as Na^+, Ca^{2+} and K^+, with α7nAChR showing the highest permeability for Ca^{2+}. As well as channel activity, a number of other intracellular events and various downstream signaling pathways can also be regulated by nAChRs, such as Ca^{2+}/calmodulin, mitogen-activated protein kinase (MAPK), protein kinase C and vascular endothelial growth factor (VEGF) (4-6). Different nAChR subtypes also have roles in control distinct physiological processes, such as maintenance, metabolic tone and control of carcinogenesis.

nAChR genes are expressed not only in neuronal systems, but also in numerous non-neuronal tissues cells such as skin, pancreas and lung, suggesting that nAChRs may have roles in other biological processes in addition to synaptic transmission (7). In fact, nAChRs have been found not only to perform their classic function at neuromuscular junctions, but also to function in the regulation of cellular processes such as cell proliferation (7) and cell death (1,3,8). Decreased survival rates in cancer are believed to be affected by the nAChR pathway activation, influencing tumor cell proliferation, apoptosis (3,8), proinvasive and angiogenic phenotypes (9) and epithelial-mesenchymal transition (EMT). This review summarizes the current evidence of the role of nAChRs in types of human cancer.

2. Lung cancer

Tobacco smoking is known to be the major cause of lung cancer worldwide (10). Numerous large genome-wide association studies have found an association between single-nucleotide polymorphism (SNP) variation at 15q24-15q25.1 and susceptibility to lung cancer (11-18). There are three nicotine acetylcholine receptor (*CHRNA*) genes at this locus. Studies from the International Agency for Research on Cancer (Lyon, France), the MD Anderson Cancer (Houston, TX, USA), and deCODE Genetics (Reykjavik, Iceland) have shown that there is a nearly 14% increase in lung cancer susceptibility associated with nAChR cluster variations, regardless of

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Key words: nicotinic acetylcholine receptor, cancer, tobacco

smoking status (12). In addition, a non-synonymous variant, rs16969968, in *CHRNA5*, which results in an amino acid substitution (D398N) in the second intracellular loop of the protein, can increase lung cancer risk >30% (12). In the *CHRNA3*/*CHRNB4* intergenic region, the SNP rs8023462 can interfere with *CHRNA3*/*CHRNB4* gene expression by interacting with GATA transcription factors (19). Overexpression of *CHRNA3* by ectopic expression was shown to induce apoptosis (20). Knockdown of *CHRNA3* by short hairpin RNA (shRNA) in lung cancer cells abolished the response of the cells to apoptosis-inducing agents, suggesting the importance of this gene in human cancer (20). *CHRNA3* knockdown may result in overexpression of *CHRNA7* and *CHRNA5* (20), while abnormal *CHRNB4* methylation was found to be insufficient to induce significant silencing of the gene, and could not downregulate gene expression. One study in 28 squamous cell carcinomas (SCCs) of the lung showed increased levels of CHRNA5 and CHRNB3 transcripts, together with higher ACh levels, which is associated with increased levels of choline acetyltransferase transcripts and decreased levels of cholinesterase transcripts. Incubation of the H520 SCC cell line with nicotine increased ACh secretion, expression of nAChRs (α7 and β4), and activity of those expressed nAChRs. Darifenacin, an M3 mAChR-selective antagonist, was able to abolish the proliferative effects of nicotine and ACh on lung cancer growth by downregulating the activation of MAPK (21). Human non-small cell lung cancer (NSCLC) tissues and cancer cells were shown to express α7-nAChR (22). Nicotine can cause Ca^{2+} influx into lung cancer cells by binding to α7nAChR and triggering membrane depolarization, which activates voltage-gated Ca^{2+} channels and subsequently activates the MAPK pathway, which may result in increased expression of the B-cell lymphoma-2 protein and downregulation of apoptosis (23). Subsequently, the MAPK pathway activates the transcription factor nuclear factor-κB (NF-κB) and promotes cancer cell proliferation. Expression of α7-nAChR is also associated with activation of the Rb-Raf-1/phospho-extracellular signal-regulated kinase (ERK)/phospho-p90RSK pathway. In certain cases, α7-nAChR antagonists were able to inhibit proliferation of human NSCLC cells via mitochondria-associated apoptosis (22). Expression of the β2 and β4 nAChR subunits was also been found in all adenocarcinoma (AC) and SCC tissue samples; in ACs, all α5, α7, β2 and β4 nAChR subunits were detected in glandular structures, while in SCCs, the α5, β2 and β4 subunits were mainly expressed in tumor cells at invasive fronts (24). α7 nAChR inhibited cell proliferation in well-differentiated NSCLC cells, but promoted cell proliferation by mediating the pro-proliferative activity of nicotine in poorly differentiated NSCLC cells (24). The α7 nAChR and heteromeric $\alpha5^*\beta2^*\beta4^*$ nAChRs are involved in tumor progression by stimulating invasion and regulating proliferation (24). Li *et al* (25) reported that nicotine can promote tumor growth and cause resistance to erlotinib in the PC9 xenograft model by activating the α1 nAChR and epidermal growth factor (EGFR) pathways. In A549 cells, use of shRNA or the selective antagonist methoctramine to block M2 mAChR (M2R) signaling resulted in inhibition of tumor cell proliferation *in vitro* and *in vivo*. Blocking of M2R signaling decreased MAPK and AKT phosphorylation. Further studies indicated that M2R signaling also promotes EMT *in vitro* and *in vivo* (26). Chernyavsky *et al* (27) reported that cell membrane (cm)-nAChRs could promote growth of lung cancer cells, and could also promote growth factor signaling [α7 cm-nAChR synergizes with EGF, α3 synergizes with VEGF, α4 synergizes with insulin-like growth factor I (IGF-I) and VEGF, and α9 synergizes with EGF, IGF-I and VEGF]; and simultaneous activation of cm- and mitochondrial-nAChRs produces a combination of growth-promoting and anti-apoptotic signals. Activation of M3R by ACh was also found to promote cell proliferation, invasion and migration of lung cancer cells by activating the EGFR/phosphoinositide-3-kinase (PI3K)/AKT pathway and interleukin-8 (28). Recently, it was reported that cyclooxygenase-2-derived prostaglandin E2 increased α7 nAChR expression in NSCLC cells, and this effect was regulated by Jun kinase, PI3K, and protein kinase A signals (29). This finding shows a novel link between prostanoids and cholinergic signaling (29).

3. Other cancers

Tobacco smoking is also a risk factor for pancreatic cancer. Studies have shown that nAChR activation can enhance pancreatic tumor-promoting events, and that multiple pathways are involved (30). Nicotine treatment causes a significant reduction in expression of GATA6 and Mist1, both of which are regulators of acinar cell differentiation. Nicotine treatment can not only induce de-differentiation of acinar cells, but can also increase pancreatic progenitor cell activity, by increasing expression of the stem cell genes *Sox9* and *ALDH* and enhancing cancer stem cell populations. All the effects of nicotine occur through activation of α7 nAchR, followed by activation of the AKT and MAPK signaling pathways (30). As in the nervous system, nAChRs have roles in regulating the synthesis and release of catecholamines in normal pancreatic ductal cells and in pancreatic cancer cells. Nicotine was shown to induce catecholamine secretion, which was dependent on the α3, α5 and α7 nAChR subunits (31-33). Additional studies also found that in pancreatic cancer cells, nicotine activated ERK1/2, a well-known proliferation and survival-related signaling pathway (34-36).

Nicotine also inhibits γ-aminobutyric acid (GABA) synthesis and secretion in normal pancreatic cells and cancer cells in a time-dependent manner. GABA is able to inhibit pancreatic tumor growth *in vivo* and *in vitro*, which can be facilitated through the α4 nAChR subunit (31,33,37). In addition to its proliferative effects, nicotine promotes migration and invasion of pancreatic cancer cells by upregulating the mucin MUC4 in the CD18/HPAF pancreatic cancer cell line (38). The nicotine-induced increase in MUC4 expression is dose-dependent, acting through α7 nAChR activation and subsequently activation of Janus kinase 2, signal transducer and activator of transcription 3 (STAT3), and ERK1/2 (38). Nicotine treatment also enhances the association of the MUC4 promoter with the transcription factors E2F1 and STAT1 (39).

Through induction of osteopontin (OPN) synthesis and secretion, nicotine can also promote cell proliferation and metastasis in pancreatic cancer cell lines. Studies on pancreatic cancer cell lines showed that treatment with nicotine

resulted in increased proliferation and concomitant OPN gene promoter activation, mRNA expression and protein secretion (40). This effect occurred via nAChR receptor activation, with subsequent phosphorylation of ERK1/2 (40). It has also been found that nicotine-mediated migration, invasion and metastasis of pancreatic cancer cells is dependent on OPN, through inducing matrix metalloproteinase-9 and VEGF (41).

In gastric cancer, nicotine and nicotine-derived nitrosamine ketone (NNK) were found to enhance AGS cell proliferation significantly through α7 nAChR and β-adrenergic receptors. Nicotine promotes cell proliferation, which is dependent on Erk1/2 activation, while NNK-induced cell growth is dependent on p38 MAPK. In addition, nicotine and NNK mediates cyclooxygenase-2 induction to modulate cell cycle regulatory proteins, and contributes to cancer development. A selective cyclooxygenase-2 inhibitor, SC-236, was shown to block nicotine/NNK-induced cell proliferation (42). An *in vitro* study on the AGS gastric cancer cell line reported that when α7 nAChR was knocked down by siRNA, the cells were more resistant to 5-fluorouracil treatment (43).

ACh receptors are also expressed in human mesothelioma and normal mesothelial cells. Nicotine stimulation prompts cell growth through activation of nicotinic cholinergic receptors. Activation of α7nAChR can cause Ca^{2+} influx into cells, which subsequently activates voltage-gated Ca^{2+} channels, which in turn activate the MAPK pathway. Subsequently, MAPK promotes cancer cell proliferation through activating transcription factor NF-κB (4).

In human mammary epithelial cells, non-malignant MCF10A and malignant MCF7 breast cells were shown to express the α3, α5, α7, α9, α10, β1, β2, γ, δ and ε nAChR subunits and the M1, M3, M4 and M5 muscarinic receptor subtypes. The malignancy was associated with expression of the α1, α4 and β4 nAChR subunits and the M2 subtype. Malignant transformation of basal epithelial cells was also associated with overexpression of α7- and α9-made nAChRs. NNK upregulated ERK1/2 phosphorylation, stimulated expression of the gene encoding the tumor promoter hepatocyte growth factor, downregulated expression of the tumor suppressor gene *CDKN2A* and induced tumorigenic transformation of MCF10A cells (44).

4. Conclusion

Taken together, the obtained results provide new insight into the molecular mechanisms of nAChR-mediated oncogenic effects on types of human cancer. It is clear that nAChRs has significant roles in the pathogenesis of cancers. Further analyses of nAChRs may contribute to clinical applications in the future. More *in vivo* studies are required to confirm their oncogenic effects.

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