

## Cigarette Smoke and Breast Cancer Stem Cells

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Epidemiological studies have suggested that cigarette smoking is related to increased breast cancer risk. In agreement with this, clinical studies indicated that smoking increases breast cancer mortality and the incidence of metastasis from the breasts to the lungs [1,2]. Cigarette smoke contains over 4000 different chemicals, many of which are toxic and carcinogenic in a variety of cells, including breast epithelial cells [3]. Among them, nicotine is considered to be related to increased cancer risk. For example, nicotine has been shown to induce resistance to the chemotherapeutic drug doxorubicin in human MCF-7 breast cancer cells [4]. Moreover, this compound has been shown to release vascular endothelial growth factor, which plays a key role in angiogenesis [5]. However, limited experimental data support direct links between breast cancer and nicotine exposure. In addition, the mechanisms by which nicotine might promote breast cancer are not fully understood.

Growing evidence suggests that tumors are organized in a hierarchy of heterogeneous cell populations and are formed and maintained by a small population of stem/stem-like cells known as "Cancer Stem Cells (CSCs)" [6]. CSCs show the following characteristics: self-renewal, drug resistance, and high tumorigenicity. Only genetic mutation-induced CSCs have the ability to form tumors. Because CSCs share many molecular similarities with embryonic and tissue stem cells, all the major signaling pathways such as Notch, Wnt, and Hedgehog involved in normal stem cell biology have been implicated in CSC proliferation [7-9].

Aldehyde dehydrogenase (ALDH), a detoxifying enzyme responsible for the oxidation of intracellular aldehydes, is a functional marker for breast CSCs, and its expression is correlated with poor prognosis, increased metastasis, and chemotherapy resistance in breast cancer patients [10-12]. However, the relationship between cigarette smoke and CSCs has not yet been elucidated.

Hirata et al. [13] have recently showed that nicotine induces breast CSC proliferation by binding to their nicotinic acetylcholine receptors (nAChRs). Nicotine concentrations comparable to those reported in the plasma of cigarette smokers increased both the frequency and absolute number of CSCs, which were identified as ALDH-positive MCF-7 cells. Furthermore, nicotine-induced CSC proliferation is blocked by N-[N-(3,5-difluorophenacetyl)-L-alanyl]-S-phenylglycine t-butyl ester (DAPT), which prevents Notch signaling by inhibiting cleavage of the activated Notch receptor by  $\gamma$ -secretase, suggesting a possible role of Notch in breast CSC biology. The involvement of Notch signaling has been well characterized in breast cancer. Aberrant Notch activation has been reported in various subtypes of breast carcinoma [14], and a recent study showed that the co-expression of Notch-1 and one of its ligands, jagged-1, correlated with poor prognosis [15]. Interestingly, another study has shown that exposure to cigarette smoke extracts activated Wnt and Hedgehog pathways in bronchial epithelial cells [16]. Taken together, these data suggest that cigarette smoking could activate signaling pathways involved in stem cell proliferation. More specifically, it is possible to hypothesize that nicotine-mediated breast CSC proliferation via the Notch pathway might be involved in the progression of breast cancer. The mechanisms underlying the nicotine-mediated stem cell pathway activation remain to be determined. In addition, *in vivo* studies are required to elucidate the effects of nicotine on breast CSCs.

The  $\alpha 7$  subtype of the nAChR has been identified as the major

mediator of breast CSC proliferation [13]. Moreover, nAChR is overexpressed in breast cancer [17]. It is possible, therefore, that nicotine could stimulate breast CSCs growth via this receptor. Because targeting nAChR is considered highly selective for cancer cells, nAChR might be a good target for cancer treatment. In agreement with this, recent studies have shown that, nAChR antagonists are promising agents for the treatment of lung cancer [18]. However, because nAChR is widely expressed in various stem cells [19], the risks of unexpected side effects must be carefully assessed.

In addition to nicotine, the nicotine-derived nitrosamine ketone (NNK), 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, acts as an agonist to nAChR with higher affinity for  $\alpha 7$ -nAChR than nicotine and has been found to transform normal human breast cells [20]. Therefore, NNK is also a potential inducer of breast CSC proliferation. Future studies are required to examine which of the 4000 components in cigarette smoke are responsible for breast CSC proliferation and cancer progression.

In conclusion, growing evidence suggests that nicotine in cigarette smoke plays a key role in breast cancer. In particular, the finding that nAChR regulates breast CSCs and provides important insights into the relationship between cigarette smoking and breast cancer. The development of agents that disrupt the nAChR signaling pathway may provide a new therapeutic approach for the treatment of breast cancer.

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