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Mini review

Nicotinic Acetylcholine Receptor-Mediated Signaling Pathways in Pluripotent Stem Cells

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Electronic cigarettes (E-cigarettes) are battery-operated devices that transport a nicotine- containing aerosol or vapor by heating the liquid. The liquid usually contains nicotine, propylene glycol or glycerol, Acetylcholine receptors (AChRs) are membrane receptors that bind to the neurotransmitter acetylcholine. They are classified into two distinct subtypes, nicotinic AChRs (nAChRs) and muscarinic AChRs (mAChRs). nAChRs belong to the Cys-loop family of pentameric ligand-gated ion channels. They consist of seventeen subunits, various α (CHRNA1-10, but CHRNA8 is avian specific) and β (CHRNB1-4) subunits with δ (CHRND), γ (CHRNG) and ε (CHRNE) subunits [1,2]. These subunits can be divided into neuronal-type (CHRNA2-10 and CHRNB2-4) and muscle-type (CHRNA1, CHRNB1, CHRND, CHRNG, CHRNE). Although they form various heteromeric pentamers by combination of any α subunits and other subunits, some α subunits (CHRNA7 CHRNA8 and CHRNA9) function ashomomeric pentamers. Upon binding to ligands, pentameric receptors undergo conformational changes to open a central pore, causing the influx of extracellular ions and various cellular responses.

Table 1: Expression of CHRNA/Chrna and CHRNB/Chrnb genes in human and murine pluripotent stem cells.

	human ESCs (BG02, WA09) [10]	murine ESCs (CGR8) [11]	murine IPSCs (iPS-MEF-Ng-20D-17) [7] (unpublished data)
CHRNA1/Chrna1	+	-	+
CHRNA2/Chrna2	-	-	+
CHRNA3/Chrna3	+	+	+
CHRNA4/Chrna4	-	+	+
CHRNA5/Chrna5	++	-	++
CHRNA6/Chrna6	-	-	-
CHRNA7/Chrna7	-	+	+
CHRNA9/Chrna9	+	+	+
CHRNA10/Chrna10	+	+	+
CHRNB1/Chrnb1	+	+	++
CHRNB2/Chrnb2	-	+	+
CHRNB3/Chrnb3	+	+	+
CHRNB4/Chrnb4	-	+	+

Note: Table Abbreviations: ESCs: Embryonic Stem Cells; iPSCs: induced-Pluripotent Stem Cells.

Consistent with the findings for classification of receptor genes, nAChR-mediated signaling pathways play important roles in neuron and muscle [3]. In addition to these tissues, nAChR genes are also expressed in various non-neuronal tissues and cell types [4,5]. Pluripotent stem cells (PSCs), so-called embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs), represent one of such cell types. ESCs are derived from the inner cell mass of preimplantation embryo, whereas iPSCs are generated through somatic cell reprograming by the overexpression of defined transcription factors (Yamanaka factors) [6]. These are expected to be an ideal source for novel regenerative medicine [7,8]. PSCs have unique characteristics that undergo unlimited self-renewal and retain pluripotency to differentiate into any cell types. Various signaling pathways are involved in maintaining the delicate balance between self-renewal and differentiation in PSCs [9]. They are also important for reprograming of somatic cells to establish iPSCs. Elucidation of these pathways is essential for the clinical applications of these cells. Both human and murine PSCs express various CHRNA/Chrna and CHRNB/Chrnb genes [10,11] (Table 1). In addition, expression pattern of nAChR genes dynamically fluctuates during differentiation of PSCs into various cell lineages, including neuronal cells and myocytes. These finding indicate that nAChR-mediated signaling pathways play important roles in PSCs.

In fact, nAChR-mediated signaling pathways affect differentiation of PSCs. Triggering of nAChRs expressed in human ESCs-derived embryoid bodies by nicotine resulted in activation of MAPK and shifts of spontaneous differentiation toward hemangioblast [12]. In contrast, Gue et al. reported deleterious effects of nicotine on human ESCs-derived various lineages, including cardiomyoctes, by using single cell RNA-sequencing [13]. Consistent with the results in human ESCs, nAChR-signaling pathways inhibit differentiation of mESCs into cardiomyocytes by suppressing cardiac genes via DNA methylation [14]. Doubling time is reduced by nAChR-mediated signaling via downregulation of N-myc expression during differentiation of primate ESCs into fibroblasts [15]. Taken together, it is conceivable that effects of nAChR-mediated signaling pathways on differentiation of PSCs are dependent on the cell lineages.

In addition to the differentiation processes, nAChR-mediated singling pathways likely contribute to self-renewal and establishment of PSCs. Because murine and human ESCs express choline acetyltransferase and synthesize ACh [12,16], nAChR-mediated signaling pathways should be constitutively activated in PSCs. In support of this hypothesis, exogenous Ach and nicotine additions affect the proliferation and survival of PSCs via nAChRs. Nicotine increases DNA synthesis via some Chrna pathways in murine iPSCs [17,18]. In murine ESCs, high doses of ACh and nicotine reduce apoptosis, but they inhibit proliferation [19]. In contrast, it is unknown whether nAChR-mediated signaling pathways are involved in the undifferentiated status, pluripotency and reprograming process. To achieve a comprehensive understanding of the roles of nAChR-mediated signaling pathways in PSCs, it is necessary in future studies to investigate the functions of each CHRNA/Chrna and CHRNB/Chrnb gene that are expressed in PSCs. It is also important to evaluate nAChR-mediated signaling pathways that are activated not only by exogenous ligands, but also by endogenous ACh. Such studies will provide essential insights to ensure the use of PSCs in future regenerative medicine.

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Conflict of Interest

All authors have nothing to disclose.

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