



COMMENTRY

Ethanol and Stem Cells

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ABSTRACT

Many studies have showed disadvantageous effect of ethanol exposure on stem cells. Ethanol exposure during development leads injury to various types of stem cells including neural stem cells (NSCs), dental pulp stem cells, mesenchymal stem cells, embryonic stem cells and etc. Because NSCs play a basic role in the development and maturation of the central nervous system, it is vital to understand the effect of ethanol on NSCs differentiation. Additionally, alcohol misuse appears lead to periodontal disease, tooth decay and mouth wounds that are potentially precancerous. Individuals who abuse alcohol are at high risk of having seriously destroyed teeth, gums and compromised oral health in general. Some of these adverse situations maybe are because of ethanol effects on stem cells. Therefore, here, ethanol effects on the various types of stem cells were reviewed.

Keywords: Alcohol, Ethanol, Dental pulp stem cells, Neural stem cells, Bone marrow-mesenchymal stem cells

Introduction

Ethanol (EtOH), also generally called ethyl alcohol, drinking alcohol, or simply alcohol is the main type of alcohol found in alcoholic drinks, generated by the fermentation of sugars by yeast. It consider as a drug which is neurotoxic psychoactive and one of the oldest recreational

drugs used by individuals. It can cause alcohol poisoning when used up in sufficient quantity [1]. EtOH is a central nervous system (CNS) depressant and has significant psychoactive effects in sublethal doses. Based on its abilities to alter human caution, EtOH is considered a psychoactive drug [2].

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EtOH kills organisms by denaturing the proteins and dissolving the lipids and is also effective against most bacteria, fungi and viruses, but is ineffective versus bacterial spores. Often in surprisingly great concentrations, is used to dissolve many water-insoluble drugs and related compounds. Appropriative liquid procurements of cough and cold medications, analgesics, and mouth washes may be dissolved in 1 to 25% concentrations of EtOH and may need to be eluded in individuals with adverse reactions to EtOH such as alcohol-induced respiratory reactions. The amount of EtOH in the body is typically quantified by blood alcohol content (BAC). At higher concentrations, EtOH operates as a CNS depressant, producing at progressively higher dosages, impaired sensory and motor function, slowed learning, confusion, unconsciousness, and possible death. EtOH is commonly consumed as a recreational drug, mostly while socializing, due to its psychoactive effects [3, 4].

Stem cells are responsible for preparing a continuous supply of healthy cells during our lifespan. Aging cause that stem cells become less effective because of the buildup of damaged DNA [5]. Several studies have identified a key source of this DNA damage and defined two protective mechanisms that stem cells use to counteract this threat. Research in mice has demonstrated that this DNA damage is normally kept in check by two vital control mechanisms: an enzyme that clean up the toxic breakdown product and a set of proteins that recognize and repair damaged DNA. Mice lacking both these protective systems develop bone marrow failure, due to obliteration of their blood stem cells [6].

Scientists have found that stem cells are extremely sensitive to the main byproduct of alcohol, i.e. acetaldehyde, which causes irreversible mutation to their DNA. This finding may also be significant in individuals who are deficient in the enzyme called alcohol dehydrogenase (ALDH2) that removes toxic acetaldehyde and, therefore, might be unusually

susceptible to DNA damage [7]. Therefore, alcohol consumption in this population may result in irreversible damage to their blood stem cells, increasing their risk of cancers, bone marrow malfunction and expedite ageing. The findings may be particularly significant for a vast number of people from Asian countries such as China and Iran; where up to a third of the populations are deficient in the ALDH2. Therefore, consumption of alcohol in these individuals could increase their work of DNA repair system that consequently causes irreversible damage to DNA of their stem cells [8]. The long-term consequences of this could be bone marrow dysfunction and the emergence of blood cancers. In addition, recent studies have suggested that drinking alcohol can kill lots of stem cells, the critical cells held in the body. By following samples of binge drinking compared to no drinking at all people, it has found that the alcohol have a noticeable effect on the stem cell count [9].

Effects of ethanol on dental pulp stem cells

Dental pulp stem cells (DPSCs) are proliferative, multipotent adult stem cells. Substantial experimental evidence indicates that stressful external environments, such as one induced by EtOH, have an important role in regulating the DPSCs fate. Because of reactive aldehyde byproducts, EtOH disposal leads to changes in DNA and proteins within cells that result in mutagenesis and cell decease [10]. Additionally, EtOH induces the hypermethylation of genes involved in cell cycle and also increases expression of DNA methyltransferases (dmt) in stem cells. These alterations affect signaling pathways induced by growth factors that subsequently give rise to down-regulation of associated mRNAs and proteins in cell cycle [10].

Alcohol misuse appears to lead to periodontal disease, tooth decay and mouth lesions that are potentially precancerous, however, it is currently not fully understood whether alcohol exposure has impact on maintenance of adult stem cells, determination of stem cell fate and plasticity, and

affect stem cells niche [10]. Recently, Khalid et al. revealed that human DPSCs derived from adult dental pulp can be directed to differentiate into osteogenic or odontogenic cells and also transdifferentiate into neuronal cells [10]. They performed Principal Component Analysis to detect expression data separation of EtOH treatment by time and by doses. Treatment time showed quite consistent grouping regardless of doses, but doses in combination of treatment time show high degree of alterations in gene expression, showing that genome-wide transcriptomic alterations is induced by EtOH treatment in human DPSCs.

Effects of ethanol on neural stem cells

Potential teratogenic impacts of EtOH on fetal development have been documented. Especially studies have shown deleterious effects of EtOH on development of neurons in animal models and on the survival rate and differentiation of neuronal precursor cells [11]. To better understand the molecular effects of alcohol on the procedure of neural differentiation, gene expression profiling have done by microarray analysis on human embryonic stem cells (hESCs) differentiated into neural progenitor cells (NPCs) and neural rosettes after treatment by EtOH [12]. To survey effects of EtOH on mouse embryonic stem cells (mESCs), it has proposed to understand cause of fetal alcohol syndrome (FAS). FAS reflects a constellation of hereditary abnormalities caused by excess maternal consumption of alcohol [13]. EtOH-induced apoptosis has been suggested as a causal agent in the appearance of FAS [14]. Mouse ESCs are pluripotent cells that differentiate *in vitro* to cell aggregates named embryoid bodies (EBs) in which differentiation capacity and gene expression profile are same to those of the early embryo development. To investigate the effects of EtOH during differentiation, mES cells were incubated on a gelatin surface in presence of leukemia inhibitory factor (LIF) that maintains

adherent undifferentiated cells or in suspension to induce formation of EBs. Findings suggest that EtOH may contribute to the pathogenesis of FAS by triggering apoptotic signals during differentiation of ESCs and deregulating early stages of embryogenesis [13].

Effects of ethanol on bone marrow-mesenchymal stem cells (BM-MSCs)

Alcohol consumption has been closely related to the formation of osteoporosis and enhanced risk of fracture [15]. The habitual consumption of significant quantities of EtOH is identified as an important factor for osteopenia and increased fracture risk in both men and women [16-18]. EtOH alters osteoblast proliferation and function *in vivo* and *in vitro* [19, 20] and inhibits the formation of early osteoblast progenitors in both murine and human cell cultures of bone marrow [21].

The most abundant stromal cell population found in adult human bone marrow is the adipocyte [22, 23]. Bone marrow stroma contains a diverse array of cell types, all of which derived from the MSCs and hematopoietic stem cells (HSCs). Despite of MSCs scarcity in bone marrow (1 in 10^2 – 10^6 of marrow cells), they have been shown to differentiate into multiple lineages after induction, as defined by quantification of gene and protein expression specific for different lineages [24, 25]. Among these multiple lineages, gene and protein involved in adipogenesis and osteogenesis are the most closely related [26]. An inverse relationship has been illustrated between osteogenesis and adipogenesis [27]. As an MSC in bone marrow stroma undergoes adipogenic differentiation, adipogenesis-related genes, e.g., adipocyte P2 (aP2) lipoprotein lipase (LPL), and peroxisome proliferator activated receptor (PPAR)-2, undergo up-regulation, whereas osteogenesis-related genes, e.g., collagen type I and osteocalcin, are down-regulated [22] and a mutual relationship also reflected in osteoporosis. In addition to a decrease in bone mass, osteoporosis is accompanied by an increase in marrow fat [28]. The adipocyte is the most abundant cell type found in

adult human bone marrow, although its precise role is unknown. Several hypotheses have been proposed to clarify the function of marrow adipocytes, including a passive role to fill the marrow cavity, an active role in lymphohematopoiesis, energy metabolism of resorbing osteoclasts, or clearance and storage of circulating triglycerides [29, 30].

The effects of EtOH on bone are primarily on osteoblasts and their progenitors [31]. Animal studies clearly demonstrate that chronic EtOH administration down-regulates osteoblast function [32]. Previous studies have shown that high blood EtOH concentrations achieved by repeated injections (i.e., a binge model of intoxication) result in up-regulation of bone resorption [33]. An *in vitro* study has showed that EtOH inhibited hMSC osteogenic differentiation by reducing collagen type I synthesis and alkaline phosphatase activity. As well as, collagen type I gene expression was down-regulated by EtOH. Because of the reciprocal correlation between osteogenesis and adipogenesis, we hypothesized that EtOH might promote hMSC differentiation toward adipogenesis [34].

In another study, it was found that adipocytes were more abundant in induced cells treated with EtOH compared with induced cells without EtOH at each time point after day 10 [35]. Among the five markers studied, only the PPAR- 2 gene was significantly up-regulated by EtOH. PPAR- 2, is a member of the nuclear hormone receptor superfamily and is considered to be a master gene in the control of adipocyte differentiation. aP2 was not regulated by EtOH at the mRNA level. However, the protein level of aP2 was significantly increased by EtOH after 6 days of treatment with EtOH, suggesting that EtOH modifies aP2 at the translational level. Also, the increase of aP2 activity further supports the hypothesis that marrow adipocytes are actively involved in the storage and clearance of circulating triglycerides. EtOH might promote the transport of circulating triglyceride to the marrow through increasing aP2 activity [35].

Conclusion

This review provides people with information about how alcohol affects their organs, especially concerning stem cells. Overall, with an increasing body of evidence confirming that the alcohol damages the stem cells besides all the other known harms, it is more important to find ways to decrease the incidence of binge drinking.

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