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Anti-Apoptotic Mechanisms of Sertoli Cells against Ethanol Toxicity

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Testicular germ cells are highly susceptible to damage from a number of toxic chemicals in comparison to somatic cells because they have higher amount of polyunsaturated fatty acids that are vulnerable to oxidation by free radicals arising from phagocytic Sertoli cells [1]. However, Sertoli cells are rich in anti-apoptotic proteins as Bcl-w and Bcl-xL compared to germ cells; therefore, these somatic cells are more resistant to apoptosis [2-4]. In previous studies [5,6], we reported the presence of enhanced germ cell apoptosis in the testes of ethanol-treated rats (ETRs) (fed with 5% ethanol in Lieber–DeCarli liquid diet) but Sertoli cells were resistant to apoptosis. This apoptotic effect of ethanol was associated with upregulation of iNOS in Sertoli and germ cells. Ethanol-induced germ cell apoptosis was mediated by a mitochondrial pathway, indicating the presence of mitochondrial damage. In addition, excessive ethanol consumption has been reported to induce mitochondrial damage in various mammalian organs [7,8]. As shown in figure 1, there are marked degenerative changes in the testes of ETRs as vacuolization and germ cell apoptosis but Sertoli cells seemed to have normal nuclear morphology. So, why Sertoli cells are resistant to ethanol-induced apoptosis? Autophagy is a lysosomal degradation of cellular components within autophagic vacuoles (AVs) by multiple forms of cellular stress, including oxidative stress, DNA damage, protein aggregates, and damaged mitochondria [9]. In a recent study [10], we detected the presence of large numbers of AVs in non-apoptotic Sertoli cells of ETR (based on TUNEL method) [11]. Most of the AVs in Sertoli cells sequestered damaged mitochondria indicating mitochondrial autophagy (mitophagy) which was confirmed by immunogold labeling of LC3, a specific marker of autophagy, around AVs. Moreover, using immunohistochemistry, there was upregulation of autophagy genes LC3 and lamp-2 in Sertoli cells compared to weak levels in germ cells. Therefore, mitophagy may be a novel anti-apoptotic mechanism against ethanol toxicity by preventing the release of pro-apoptotic factors as cytochrome c from damaged mitochondria into the cytoplasm as shown in figure 2. Ethanol-induced elevation of germ cell apoptosis may contribute to male infertility associated with alcohol abuse. Enhanced Sertoli cell mitophagy in ETR may be important for reversibility of testicular damage resulting from alcohol abuse. Sertoli cells play a crucial role in spermatogenesis by providing physical support, nutrients, and survival signals necessary for successful spermatogenesis. It has been reported that the most common alcohol-related pathological change in the testes of chronic human drinkers could probably be reversible maturation arrest of spermatogenesis. Therefore, the reversibility of ethanol-induced hypospermatogenesis and maturation arrest could be dependent on the viability of Sertoli cells through induction of mitophagy [10,12,13]. Whether there is a role for specific mitophagy genes as PINK1 or other proteins in Sertoli cell survival, is now under investigation [14].

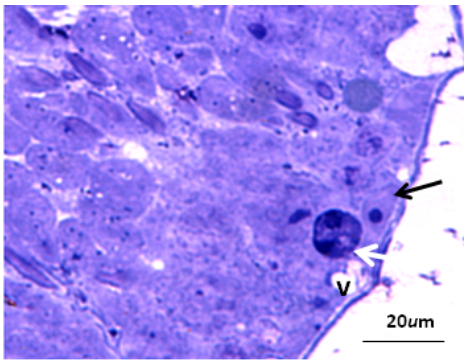

Figure 1: Ethanol-induced testicular damage. The white arrow indicates apoptotic spermatocyte while black arrow shows Sertoli cell nucleus. V, Vacuole. (toluidine blue stained, epoxy embedded semi-thin section).

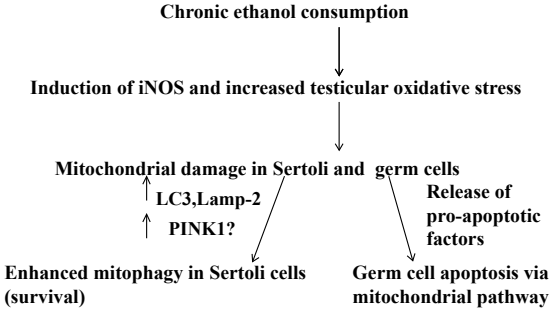

Figure 2: Mitophagy as anti-apoptotic mechanism in Sertoli cells of ethanol-treated rats. Chronic ethanol intake results in enhanced oxidative stress with subsequent mitochondrial damage. The damage of mitochondria in germ cells results in caspase-3 activation and execution of apoptosis while in Sertoli cells results in induction of mitophagy and survival [5,6,10].

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