

## Connexins as Potential Therapeutic Targets for Testis Pathologies

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Male infertility and cancers were recently linked, suggesting shared molecular bases. Because alteration of connexin functions were associated with male infertility and detected in many cancers, it is likely that connexins are one of the molecular machinery involved in the initiation of both pathologies. In addition, chemicals present within our environment can be at the origin of these two pathologies through their action on connexin expression and/or trafficking. However, taking advantage of this knowledge to develop strategies targeting connexins to cure male infertility and cancer still remains challenging.

Through its role in procreation and dissemination of the genome, reproductive function is essential for the survival of species. Since decades, accumulating evidences underline the worldwide decline of man semen quality [1-3]. This incidence will cause in the near future a major public health issue. Strikingly, male infertility was recently found as an increased risk factor for the development of various cancers, including testis cancer [4]. It is likely that the relationship between male reproductive function failure and cancer development has common molecular bases.

Connexins, the proteins that composed the gap junctions, are now seen as major molecular regulators of male fertility. Indeed, several studies demonstrated that these proteins are controlling testis function at multiple steps [5]. First of all, connexins play a central role in testis morphogenesis by controlling primordial germ cells migration [6,7], Sertoli cells proliferation [8,9], and cellular polarization within the seminiferous tubules [10-12]. Second, gap junction intercellular communications are crucial for the production of testosterone by Leydig cells in response to luteinizing hormone [13]. Third, connexins are key players for spermatogenesis. Indeed, the gap junctions located between Sertoli cells and germ cells [14] were found to be involved in meiotic progression of spermatocytes [15,16]. Forth, few studies underlined a potential role of gap junctions in erectile function (for review [17]). Due to the implication of gap junction in all these function, it is clear that a defect of connexin function will have a dramatic impact on male fertility.

As a potential molecular link between male infertility and cancer, connexins were found dysregulated in many cancers including: liver, colon, breast, lung, skin, thyroid, ovary and testis cancer [18]. The failure of connexin function in cancer cells was demonstrated to be due to gene mutation [19], altered mRNA and/or protein

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expression [20], or protein mis-localization [21,22]. Importantly, aberrant connexin localization has been reported in the majority of tumor cells and in chemically-induced cancer cells. Depending on the cancer cells, connexins were found either stacked in the Golgi apparatus [23], or destabilized at the plasma membrane leading to acute endocytosis [24]. Strikingly, forced-expression of connexin within cancer cells was shown to reduce cancerous features such as uncontrolled cell proliferation and migration [25,26] and promotes the effect of chemotherapy [27], suggesting that the failure of connexin functions is a primary defect that contributes to carcinogenesis.

Although there is now clear evidence that alteration of connexin functions within the organism could be responsible for male infertility and for cancer development, the cause of the connexin defect remains to be determined. Increasing evidence of the impact of the environment on both pathologies rises. Moreover, chemicals such as pollutants and endocrine disruptors were often associated with male infertility and cancer development. Interestingly, a large number of these chemicals were found to alter gap junction functionality [18]. As examples, we demonstrated in our laboratory that lindane and DDT, two well-known non-genomic carcinogens [28], strongly increased gap junction internalization leading to an abolishment of intercellular communication in Sertoli cells [29-31]. It is therefore likely that carcinogen exposure leads to defective connexin function in various organs and cell types and may impact on both male fertility and cancer development.

Altogether, these results underline that connexins could be seen as major targets for infertility and cancer therapy. However, since the defects are often associated with a lack of functionality, the design of therapeutic strategies has to be focused on either re-expression of the connexins or on forcing the recycling of connexins after their internalization. Unfortunately, these approaches are very challenging for clinical perspectives. Therefore, in the near future, developing high content chemical screening to identify

molecules able to stimulate connexin expression could permit to identify potential interesting drugs to solve this issue. In addition, similar approach could be used to identify chemicals able to recycle internalized connexins back to the plasma membrane by tuning the endocytic recycling trafficking. Recent studies uncovered that miRNAs can control the expression of connexins [32,33], consequently, miRNAs and/or antago-miR could also be seen as a promising strategy to restore gap junction function.

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