Chromosome Transplantation, a new approach to treat X-linked diseases

The central goal of our research is to completely correct gross mutations such as aneuploidies, deletions, duplications, or inversions responsible for many human genetic diseases. To achieve correction of these cases, that cannot benefit by classical gene therapy methods, we have introduced the concept of chromosome transplantation (CT). CT refers to the precise substitution of an endogenous defective chromosome with a normal exogenous one. CT generates euploid cells and is different from chromosome transfer in which the addition of one or a few chromosomes gives rise to aneuploid cells, which cannot be of clinical utility. Recently we demonstrate its feasibility both in mouse and human pluripotent stem cells. In our last study, we have reported the achievement for the first time of CT in human induced pluripotent stem cells (iPSCs) using, as proof of concept, reprogrammed cells from a Lesch Nyhan patient carrying a mutation in the X-linked HPRT, gene useful for the selection of the corrected cells. By inactivation of the HPRT gene in patient-derived iPSCs, this approach could be used for the correction of several X-linked disorders.

DMD/BMD are X-linked diseases characterized by mutations in dystrophin gene, resulting in progressive weakening and degeneration of muscles including the heart representing the leading causes of death. Despite extensive efforts in preclinical studies and numerous clinical trials, at present there is no a resolutive cure. The therapy for these pathologies faces one major obstacle due to the gross rearrangements account for the majority of cases (>75%). The correction of the dystrophin is difficult, if not impossible, using conventional gene therapy. Our ongoing research is focused on the correction of human iPSCs derived from DMD/BMD patients by Chromosome Transplantation which in theory could be used to treat all the DMD/BMD mutations.

References:
Keywords: Genetic Therapy; Chromosome Transplantation; X-linked Diseases; Lesch Nyhan Disease, X-linked Duchenne Muscular Dystrophy.

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