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Review Article

Down Syndrome: Regenerative Medicine Taming the Over-Expressive Trisomy (Chromosome 21) Genes

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Abstract

Trisomy silencing is an important factor in curing Down syndrome. As per a study in various experiments, XIST Transgene transforms chromosome 21 in stem cells. This Transgene normalizes cell function and development upon transformation and its induction in Transgene clones corrects the overproduction of meakayo cytes, stem cells, iPS cells and erythrocytes keeping the balance of hemopoietic developments. Given all these to added knowledge, our study further advanced to CD4/CD43 progenitors cells demonstrating principle proof for epigenetic based investigative strategy in pathology. Chapter basic focuses on drug discovery, delivery of drugs, administration path, dosage and frequency of transplantation. Monitor tools of MRI, MSK and PET-CT scanners. Also, the cultivation of chromosome 21 cells trisomy to disomy is relevant without genetic manipulation, chemical treatment and exposure to irradiation. Disomy or diploid cells serve to the purpose of drug screening and raw material of regenerative medicine and cell-based therapy.

Keywords: Down Syndrome; Regenerative Medicine; Chromosome 21; Genes.

Introduction

Down syndrome (DS) caused by chromosome 21 defects, also known as trisomy 21 values child with social abilities but with cognitive failure or disability that progresses towards adulthood, a disorder in medical conditions including congenital heart disease, susceptibility to immune risks and virus exposure, cognitive to onset to Alzheimer disease and hematopoietic abnormalities including leukemia. Mostly unknown genes out of -300 genes in DS of 21 chromosomes have three copies, all of which are phenotype. Mouse models inbred for DS phenotype; biomedical research therapies have been under progress [1]. Number of candidate genes is implicated with exception of known role of APP in Alzheimer's, chromosome 21 lay the major phenotype and holds much of gene syndrome causing general stress or cell

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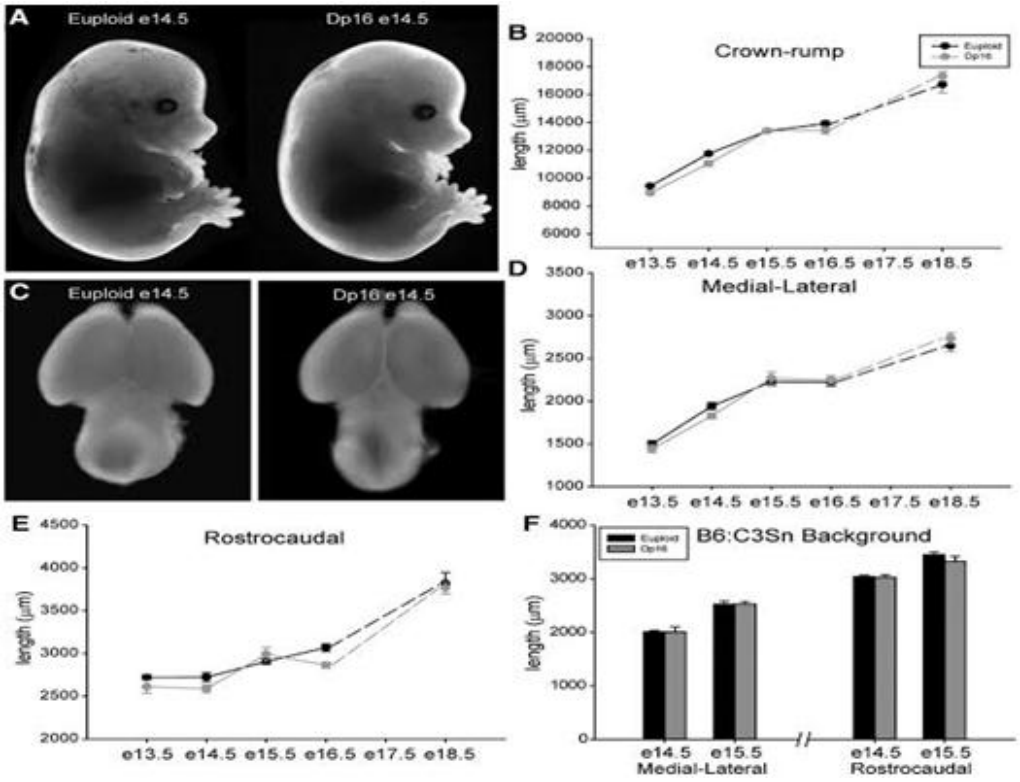
cycle defects that impact cell function and vitality. An additional copy of cells causes proliferative disadvantage, likely due to the stress in proteomic low-level over-expressive genes and specific dosage-sensitive genes [2]. Below (figure 1) indicates prenatal brain development in mice [2].

Figure 1: Effects and work of trisomy 21.



Over expression of chromosome 21 was previously demonstrated to be countered by epigenetic repression by insertion of single gene XIST into chromosome 21 controlling the nature of X chromosome inactivation of female cells in human, generating long non-coding RNA, regulating the X chromosome in cis and induces a series of chromatin modifications, silencing the transcription of X chromosomes [3]. XIST insertion silences the absence in repression throughout the autosome at comprehensive capacity. The study focus demonstrates transcriptional repression throughout the autosome, trisomy to disomy by undifferentiated iPSCs, allele-specific gene expression, CPG promoter methylating, hallmark heterochromatin and expression of gene profile all leading to show of chromosome 21 profiling from trisomy to disomy [4]. Here a key question is addressed trisomy silencing normalizes defects in cell function and pathogenesis underlining DS phenotype effectively. Assumption of XIST mediated repressed transcription would be sufficiently robust to correct cell pathogens is false, even in cells that still carry the physical presence of extra chromosome 21. Chromosome therapy's prospect determination is for the utility of an experimental approach to investigate trisomy 21 effects. In vitro testing of human fatal hematopoiesis for which phenotypes DS cellular is better characterized [5].

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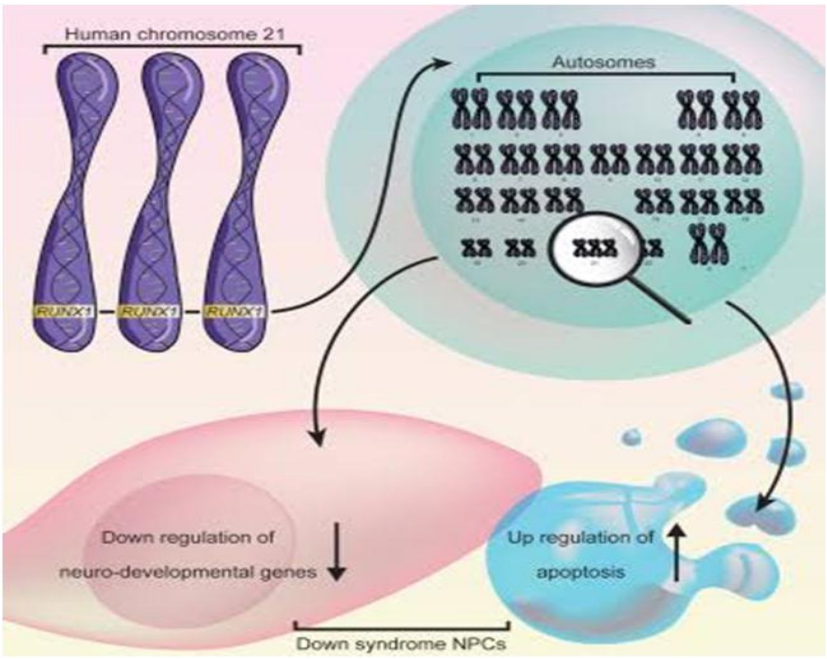
Figure 2: Shows DS therapy.



The future prospect of trisomy 21 is important in the direct determination or for the utility of the experimental approach, investigating chromosome on pathogenesis development of DS phenotypes as best characterized. The precursor of trisomy 21 is a transient myeloproliferative disorder with hematopoietic characteristics confers 500 folds greater incidence and 20-fold greater risk of acute lymphoblastic leukemia. In addition, immune defects contribute to cognitive impairment and decline [6].

Trisomy Silencing

Trisomy silencing is the major aspect of DS hemato pathogenesis of all studies comparing trisomic and disomic iPSCs providing major benchmark address XIST that largely normalizes DS related hematopoietic phenotypes [7]. Further inducible systems avoid inherent variations in distant cell clone's comparison, allowing research to extend knowledge in specific steps in hematopoiesis affected trisomy 21, also overbearing chromosomes of the same expresses CD43 progenitors but not endothelium population [8]. The approach to finding out overreactive IGF (insulin-like growth factor) is immersed in trisomy 21 myeloid disorder, further addressing the impacts of IGF signaling in GATA mutation in TMD and AMKLleukemic observed in fetal liver. Also, investigate trisomy 21 roles in cell pathology for new therapies and insights. Often developed gene therapies help in monogenic disorders and gene editing and Vivo delivery technologies. Left out progress in chromosomal imbalances, having hundreds of genes across the chromosome. However, without the insertion of single epigenetic switch or identifying pathogenic genes chromosome wide transcription effectively mitigate cell pathogenesis and normalise outcome for phenotype [9]. There is more evidence from experimentation XIST insertion normalizes down syndrome [10]. Graph 1 proves that factor [10]. Detailed (figure 4) supplies further evidence [11].

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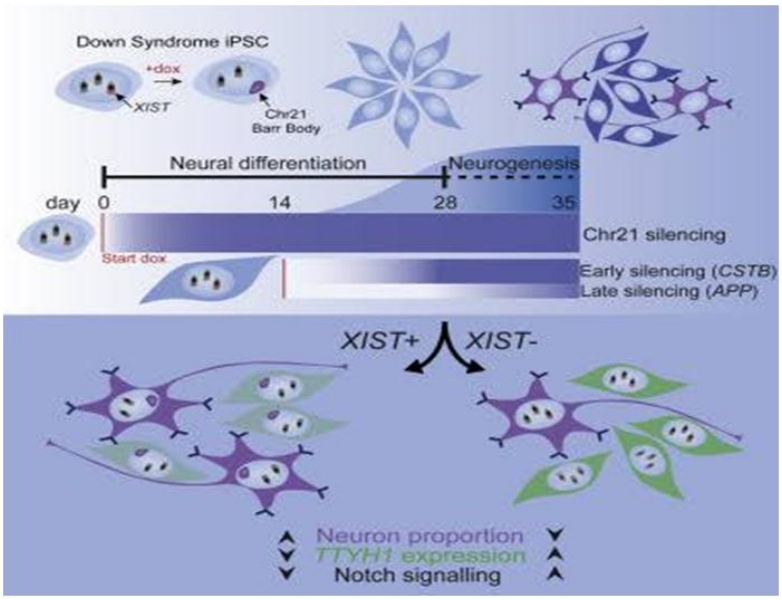
Figure 3: Shows trisomy silencing.



Graph 1: Proves that factor.

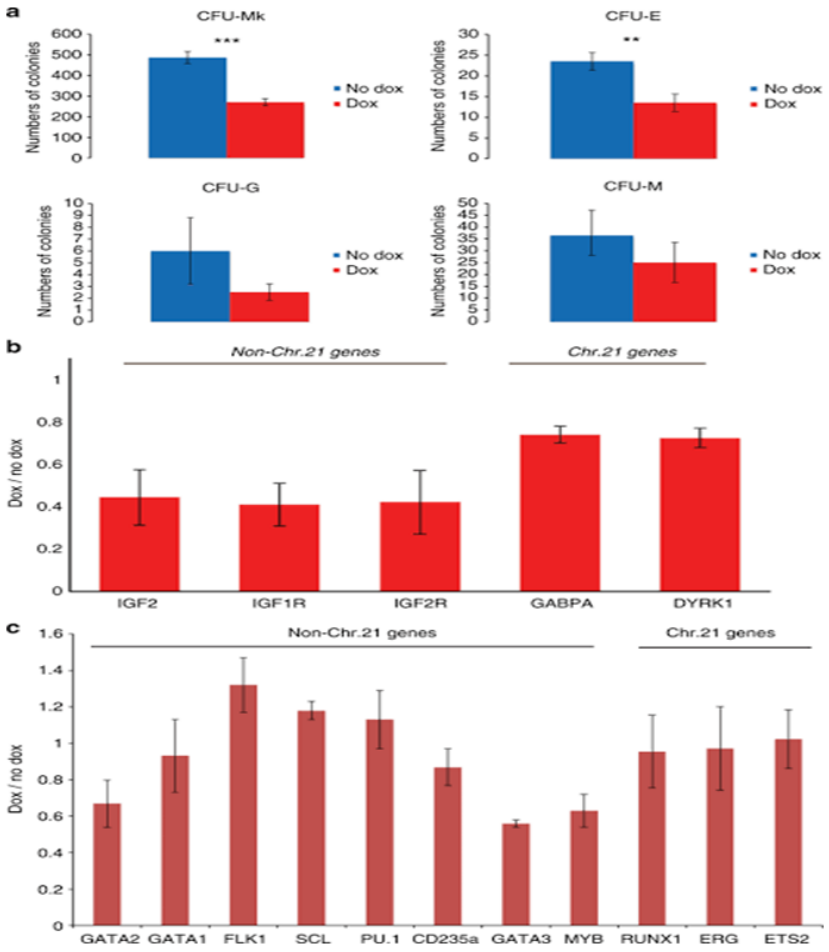


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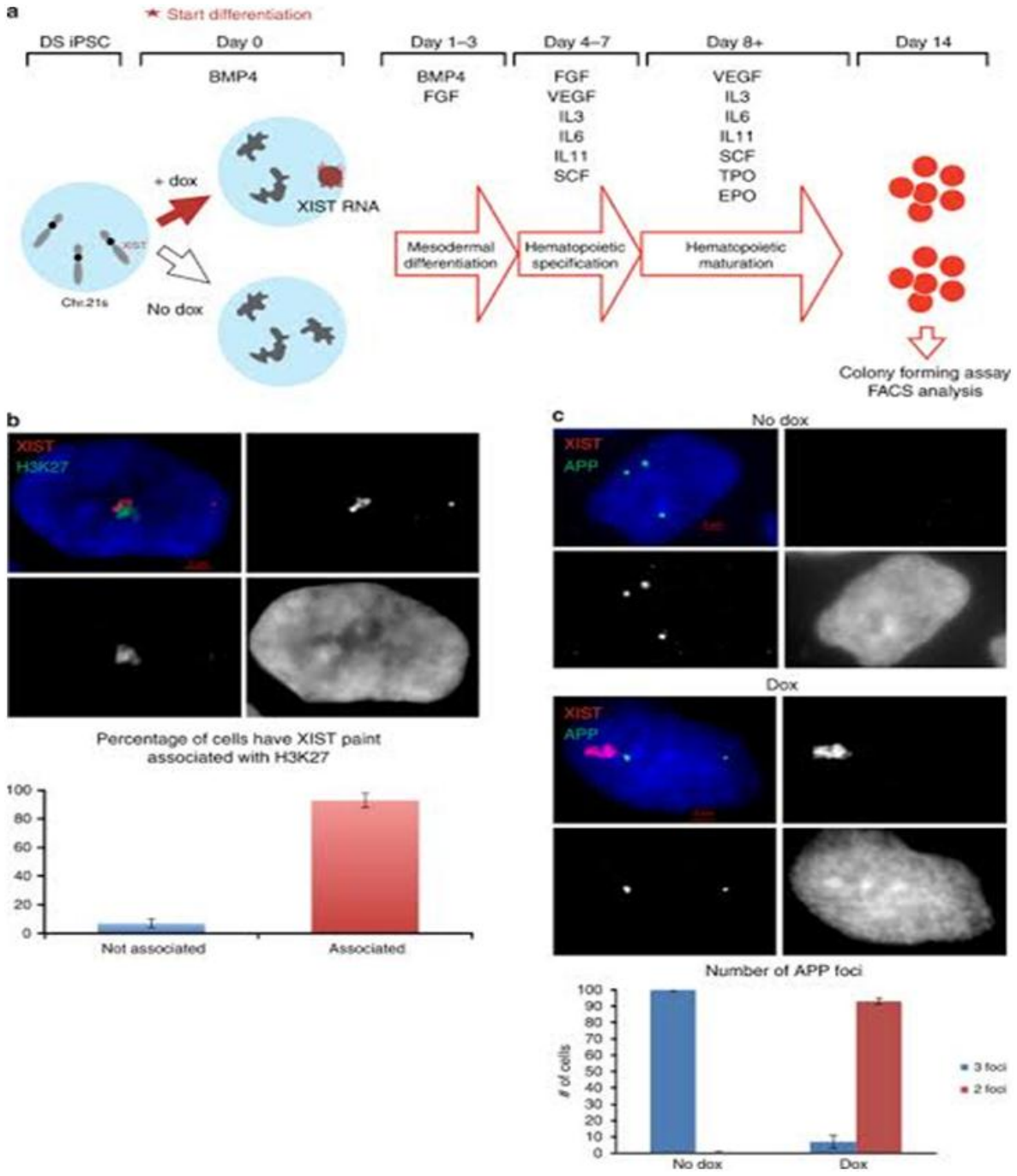
Figure 4: Supplies further evidence.



Stem cells work in trisomy 21

Stem cells injected, migrate towards injured areas of the brain. Skills attribute to the expression of growth factor and extracellular matrix receptors on the surface of cells and monocyte chemo attracted proteins, stem cell factor and IL-8. Host tissues are differentiated to replace dead neural cells through a paracrine mechanism as the halting factor continues to stimulate endogenous cells for the repair and restoration process [11]. Below (figure 5) indicates stem cells work in trisomy [11].

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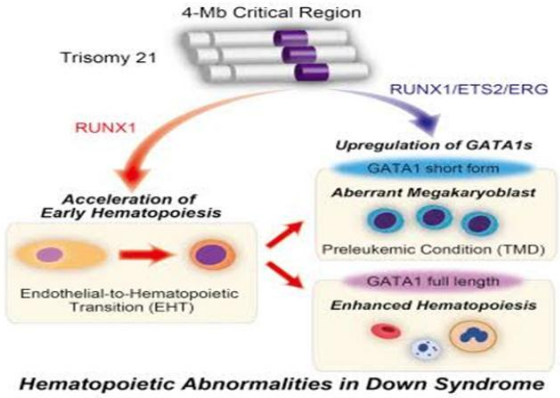
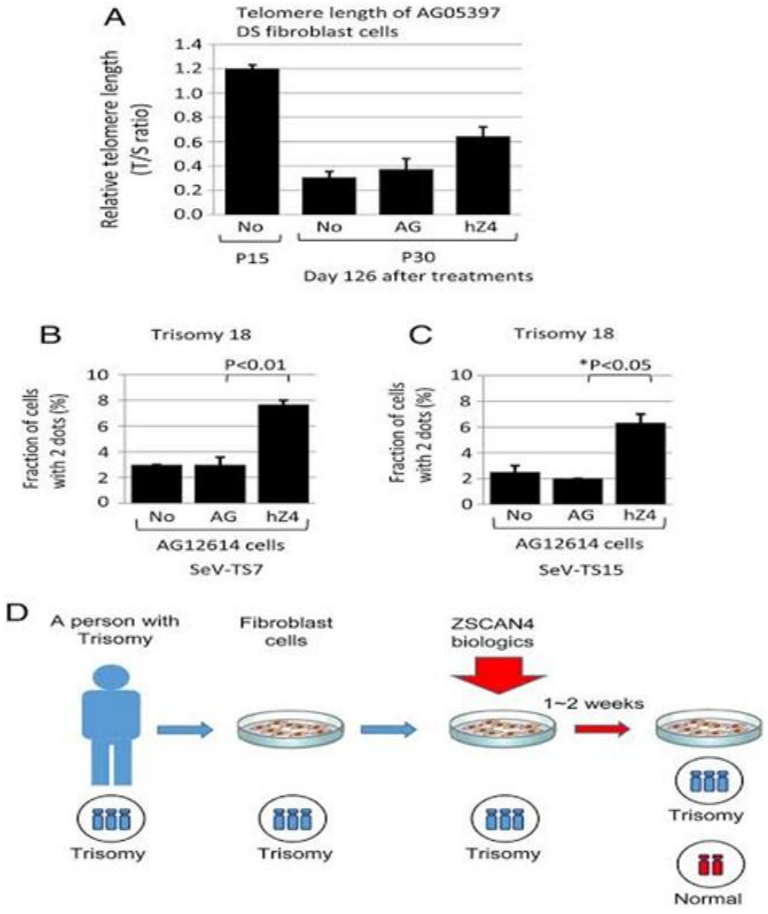
Figure 5: Indicates stem cells work in trisomy.



Regenerative cells secrete a vast array of neuroprotective growth factors, neurotrophin-3, glial cell lineage and IGF-1. IGF can induce several signaling pathways and help in enhancing differentiation. Production of vascular EGF and HGF and FDF-2 improves perfusion and enhances angiogenesis. Anti-inflammatory paracrine factors such as Interleukin and transforming growth factors help in immune modulation. Results are inevitable in (figure 6) [12].

Figure 6: Results are inevitable.



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Results

XIST cDNA was inserted in one of the three chromosomes 21 in iPSC, RNA induced transcriptional silencing across chromosome in cis, viewed in undifferentiated iPSCs. Investigation gathers steam in identifying normalization of haemopoetic cell phenotypes in trisomy silencing and subclones including four independent trisomy silencing. This helps in subcloning XIST transgenic clones, non-transgenic parental trisomic lines and isogonic disomic subclone. This system compares the effects of reducing trisomy 21 in the overexpression cell population and minimizes isogonic clone variations [13]. Effects of hematopoiesis are considered once an expression of transgenic XIST enhances the proliferation of iPSC and forms neural progenitors. XIST expression has not been found toxic and proved effective in cell proliferation and also viability, through various experimental studies. Earlier study effects to trisomy silencing causing rippling effects of study in the kinetics of neural stem cell formation and highlight developmental defect, a known deficit of neural stem cells is not an established phenotype of DS. The kinetics was not an apparent study in trisomic and disomic iPSCs, only general variability was found. Hence concluded trisomy silencing increases proliferation and production of cell types and also decreases hematopoietic overproduction cells in DS children [14]. Silencing has its advantages such as normalizing the production of CFU- Mk and CFU- E. Increase production of erythrocytes elevates risks for TMD in DS children. The adopted protocol shown mini micfetalhematopoiesis differentiated iPSC through embryonic bodies. Various experiments show XIST silencing usually takes 4 days upon induction, hence confirmation of XIST RNA localisation and chromosome silencing along with APP transcriptional factor for XIST- coated chromosome [15]. As soon as disaggregated cells using marker CD34 broadly use for lineage enrichment, XIST- positive CD34 cells are 90%exhibited in a well-localized XISTRNA accumulation and H3K27ME3 across the chromosome, silencing of APP transcription focus from the targeted chromosome. Culture utilized both transgenic subclones and non-transgenic parental trisomic line and disomic subclone. However, studies have shown D5trisomic generates iPSC sin large number along with erythrocytes and megakaryocytes colonies, with parallel induction of multiple isogonic transgenic D5 iPS lines that do not possess XIST induced trisomy 21 silencing factor inducing granulocytes and monocytes. On repeated experimental procedure error stand at <0.01, **<0.001 and P<0.5 [16]. Target addressed to express induced XIST expression and minimize the results of euploid cells and bring in a balance of hematopoietic cell types. The progenitor cells forgo colony-forming cell assays and fluorescence-activated cell types to examine the end state of assays. Below (Figure 7) compares human and rat model XIST transcription [17].

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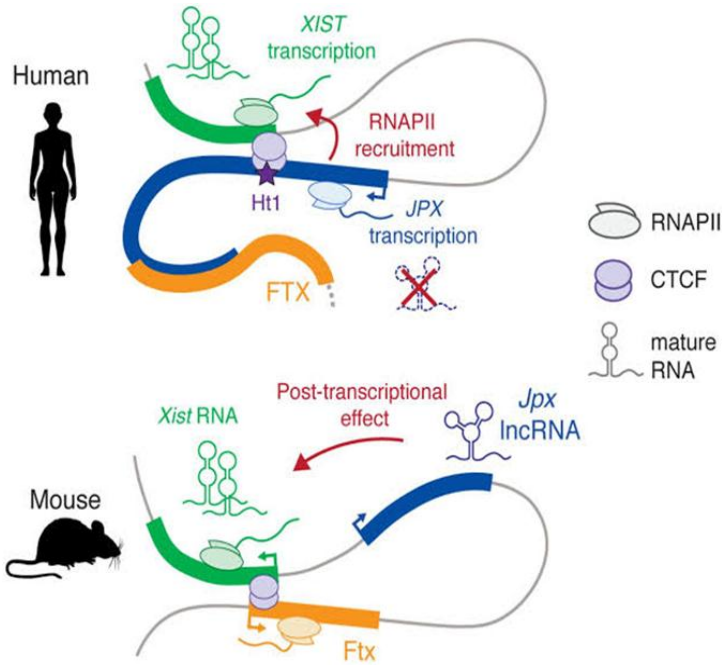
Figure 7: Compares human and rat model XIST transcription.



The doxycycline treatment of non-transgenic parental lines show no significant production in all types of cell colonies, confirming all the effect is due to XIST expression silencing chromosome. There is a parallel notable reduction in megakaryocytes and erythrocytes for all the clones during XIST expression and mirror results from comparisons of trisomic DS versus normal iPSCs. Thus, cellular phenotypes can be normalized by mitigated XISTRNA chromosome silencing. Thus, the result [18]. There are two conclusions, trisomy 21 has a significant factor on CFU-Mk and CFU-E but has no clear effect on monocytes and granulocytes. Cell population comparison provides an opportunity to detect XIST areas and results indicate a reduction in granulocyte colonies due to the silencing of chromosome 21. Single pairwise comparison was difficult to be detected when pushed towards all pairwise comparison of trisomy versus disomy showing low numbers in CFU-G, and also the lesser degree of megakaryocytes and erythrocytes. Several studies put forth as data showed very small differences in three replicate experiments of four clones each resulting in monocyte production being large lyun affected [19-21]. Thus, the overall result shows XIST- mediated silencing of 21 in DS normalizes over the production factor of CFU-Mk and CFU- E and shows proof of the feasibility of single gene insertion correct pathogenesis of phenotype with high leukemia [20].

IGF signaling and CD43+ production in excess

Changing the expression of genes was the best option in silencing chromosome 21. Hematopoietic stem cells specified character to observe trisomy 21 were tested to discern consistent changes in several panel of genes tied up to IGF signalling [21]. The mechanism of trisomy 21 leading to overproduction of mega karyocytesand erythrocytes remains a major question in

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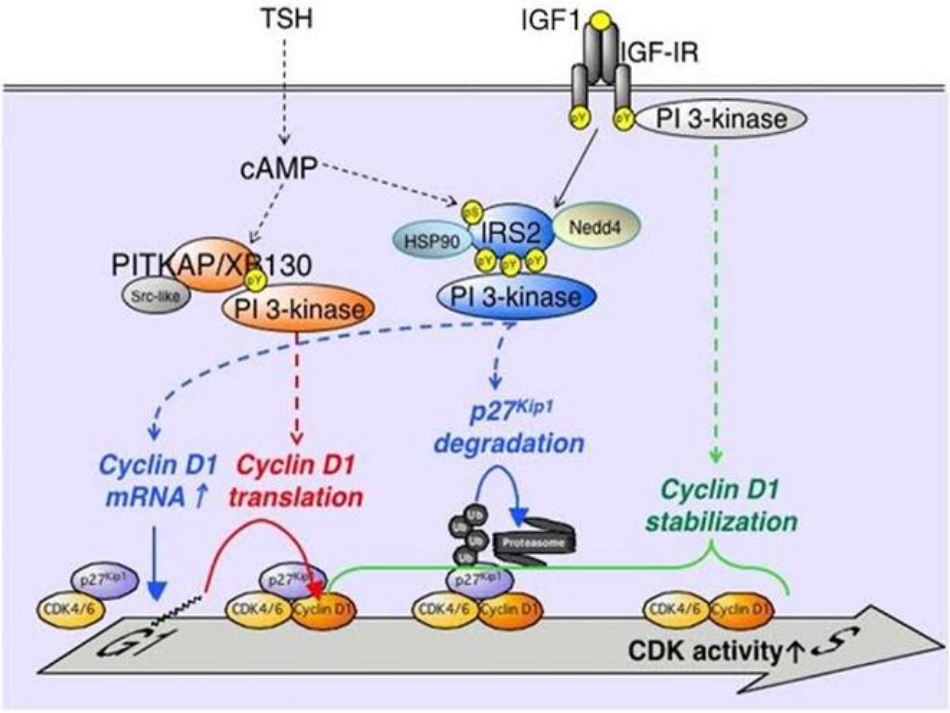
the developmental pathway in IGF expression. IGF pathway is well established to avoid impact on the proliferation of cells and hold a key alignment to various cancer cell type sand fetal hematopoiesis and DS associated cells such as DS- AMKL (especially sensible to IGF signaling). IGF signaling is most sensitive to cancer cells because of its distinguishing capacity of trisomy and disomy [22]. RT-qPCR was performed on RNA of CD43 cells with three parallel cells and three independent cultures with and without XIST, no significant patterns emerged. Many genes, highly dynamic ones have the potential to contribute towards trisomy 21 hematopathology. For chromosome 21, mRNA levels are reduced to 1/3 size, and genes GABPA helps in silencing 21. It is the same genes that are contributing towards the sensitivity to detect such systems and hold a wide range of regulators in heterogeneity and hematopoietic cell population. The sensitivity expressed in undifferentiated iPSC shows increased IGF signaling in the trisomic versustrisomy states marked by downregulation of silencedCD43+ cells [23]. Now it is an inhibitor (PPP) to examine three flow states and its effects of hematopoietic population. The experiment conducted, revealed complete elimination of CD43+ cells on low concentration, but in high concentration, the cells had very little impact. Hence inhibitor proved it to be an important factor in non-toxicity to cell proliferation and shows the presence in IGF signaling (Figure 8)[23]. IGF signaling is essential for hematopoiesis in both normal and trisomic states [24].

Figure 8: Inhibitor proved it to be an important factor in non-toxicity to cell proliferation and shows presence in IGF signalling.



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Methods

XIST mediated chromosome slicing system, iPSC culture, neural differentiation, RNA fluorescence, hematopoietic differentiation, flow cytometry, RT-qPCR, IGF signaling inhibition and analysis [23-25].

Discussion

zIt is known from several experiments, inserted XIST- cDNA often represses transcription of chromosome 21 in trisomic iPSCs, silencing and mitigating pathogenesis of DS cellular phenotypes. It is demonstrated that complex regulatory mechanisms in the hematopoietic cell pathologies can be corrected by XIST Transgene. Also, another finding is of trisomy silencing achieved by XIST induced expression from chromosome 21 reducing the over production of mega karyocytes and erythrocyte colonies in multiple transgenic clones in progenitors but did not show any change in CD34/ CD43 population. XIST expression proves it does not suppress iPSC or neural cells proliferation. Furthermore, all the result strongly supports XIST normalised hematopoietic process rebalancing dosage sensitive chromosome 21 genes. Given circumstances, developmental pathogenesis is normalised by XIST trisomy silencing. From several studies, comparing trisomic and normal cells, chromosome 21 silencing effects progenitors that are produced excessively, but no results in HE enriched population for the two markers. There has been hyper proliferative defect in EHT population which produces CD43+ progenitors. An enhanced EHT fits in chromosome 21 gene RUNX1, that commits to the production of hematopoietic progenitors fro HE. There are few chromosomes 21 genes that contribute towards the proliferation process taking advantage of brief post EHT interval prior to assay. Results also reports IGF signalling in leukemic cells are over reactive for DS, therefore there has been increased expression of iGF signalling related non chromosome 21 trisomic hematopoietic cells. There has been evidence to show production of CD43 progenitors is reacting to IGF signalling inhibition and effect is high in trisomic cells before silencing. This plays a major role in enhancement of IGF signalling in fetal haematopoiesis is and major contribution to trisomy 21 formation of CD43 progenitors, strong implication in gene RUNX1. All of above suggests a potential link between gene dosage and IGF signalling demonstrating effects of trisomy 21 in non-leukemic hematopoietic progenitor cells. It is evident that non leukemic hematopoietic progenitor cells GATA1 mutation contributes towards trisomy 21, showing its potential to enhance IGF signalling. Further knowledge provides GATA1 and trisomy 21 would push proliferation-pathway to dangerous levels causing leukemia or TMD. IGF signalling shows to contribute towards metabolic changes in the cells causing diabetes and obesity. Adding to curiosity of chromosome21 findings, chromosome silencing can lead to normalisation of DS cell phenotype. Many experiments have proved TMD and DS occur simultaneously. The risks lay the same, although TMD has less substantial morbidity. Progress is huge on developing human HSCs from iPSCs for therapeutic purposes in curing DS in children also bone marrow transplantation from HSC that is genetically modified is

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also another stream of work actively pursued in order to get HSCs more accessible. Now it is clear that XIST can initiate chromosome silencing in hematopoietic progenitors' cells, it is the dosage for chromosome 21 expression. The blood system has impacted trisomy 21, the lymphoid system cause 20-fold increase risk to cause leukemia. The focus was on myeloid differentiation, hematopoietic progenitors give rise to cells in lymphoid system. Any further progress to shut the transcript to me might give rise to lymphoid system. But progress to rise might lead to immune defects, inflammation and neuro degeneration. Also results have shown some links between then leading to Alzheimer disease prevalent in DS. Knowledge on trisomy effects on different cells will help evolve drug targets. Chromosome therapy would be added advantage in silencing genes across chromosome 21, giving complexity in unnerving complex biology of triplication of 300 genes. Foremost thing in gene therapy is coercing gene mutation correction to show normalisation of DS. Hence XIST mediated chromosome was put in place, although they are not traditional method in correction of gene mutation. Although target is not known, DS cellular phenotype correction was shown to be achieved by XIST potential and approach. There are several challenges in further development of XIST Transgene for chromosome therapy. The results budge into ongoing gene editing technology, insertion potential of single gene to mitigate some effects in trisomy 21, cure dosage imbalances and pushes for further testing and development.

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