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Potential therapeutic Strategies and Its Application in Correcting Birth Defects, Craniosynostosis, Neurological Disorders and Other Diseases

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Abstract

Background: Gene Therapy (GT) aims to fix a disease linked with genetic abnormality. Gene Therapy (GT) is currently receiving an attention from scientists, clinicians and the general public in an attempt to correct genetic defects. It including with congenital abnormalities, craniosynostosis (syndromic and nonsyndromic), craniofacial deformity, and neurodevelopmental disorders. However, its application is beset with complications partly because of lack of advanced knowledge, research and partly because of vested interest by the society.

Objective: This study is an attempt to highlight some of the major benefits of gene therapy which leads to define the role played by medical informatics in facilitating rational use of gene therapy.

Materials and methods: An attempt was made to review major studies in the international literature to synthesize the potential risks, benefits of gene therapy. We also reviewed the tools and techniques in this field of medical informatics. Which can be employed for spreading awareness about gene therapy among common people? We developed a conceptual model of matching the key concepts with the current protocols used in the field of medical informatics.

Results: GT offers a new hope for the treatment of birth defects, neurodegenerative disorders like Huntingtons disease. Its application in Parkinsons disease has moved a step closer to acceptance in the wake of its successful double blind clinical trial. The educational media, fall under four categories, viz., audio media, the visual media, the audio-visual and the virtual-media in *vitro* and *vivo*. The simulation and animation capabilities of the media are quite helpful in the conceptualization of gene therapy. The audio-visual media are useful for counseling in matter of genetic disorders the public.

Conclusion: Our study suggests that an integrated and holistic approach of medical informatics. It can be highly beneficial for the advanced application of gene therapy in the years to come. GT has become debatable and often controversial because of tendency to use for manipulating the desirable attributes. Moreover, its rational use is likely to benefit the mankind.

Keywords: Birth defects; Gene therapy; Molecular medicine

Introduction

Now a day's congenital defect, birth defects, craniosynostosis (syndromic and nonsyndromic) craniofacial abnormalities developed day by day. Its etiopathogenesis still unclear. In our experience, Nonsyndromic Craniosynostosis (NSC) is more commonly encountered than Syndromic Craniosynostosis (SCS). Particularly, in these types of cases surgery is more essential. Otherwise infants are died, because of sutures and ossification of primary and secondary. In presentscenario developing of the molecular biology a new and very innovative consepts are coming to controlling these disease. The etiopathogenesis, neuro-cognitive impairment stated and we specifically observed in our day today experience in these diseases these infants are suffering in mutations (point, substitutional, deletion, addition, allelespecific, missense and haplotypes) [1].

This contributes to premature suture fusion. An idea germinating in these concepts in experimental observations to overcome this globally burden. We are trying to develop and targeting genetic therapy to prevent pathologically sutural fusion and at the same time other defects by birth [1]. TNFRSF11B plus Vitamin-D Deficiency in infancy was associating with severs JPD [2] which complicated by craniosynostosis. Panidornate treatment with Vitamin-D sufficiency can be effective therapy for the skeletal diseases. It caused by the OPJ deficiency form of JPD.

NEL-Like molecule 1 (Nell 1) is a patent osteogenic factor. It is associating with craniosynostosis. Adeno viruses are the most commonly used viral oesteogenesis. The lanti viruses can serve as ideal vectors for gene therapy for bone regeneration. Basically there are two lanti viral vectors (Lv NELL 1 and Lv BMP2). Researcher observed that these genes transfer in hADSCs may be a novel and potential approach for bone regeneration [3].

NELL 1 is able to promote the osteogenic differentiation. The hPDLSCs, may be related to the down regulation of MSX2 expression. Lentil transfection used during in vitro gene therapy for periodontal regeneration [4]. However Beare- Stevension cutis gyratra Syndrome (BSS) is a human genetic disorder. This corrected by skin and skull deformities. BSS is by mutations in the FGF Receptors (FGFR2). Molecular mechanisms that induce skin and skull abnormalities are remaining unclear.

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We found that ligand-independent phosphorylation of FGFR2 and potential activation p38 signaling is mutant skin in calvarial tissues [5]. In our experience the pathogenic role for this activation lead to development of therapeutic strategy for BSS and related condition of acanthosis nigirinicans or craniosynostosis.

Gene environment interaction could not support a therapeutic intervention based on this interaction [6]. In our experience, sagittal synostosis is safely treated with endoscopic suturectomy and helmet therapy [7].

The molecular basis of HR-ALL is multi factorial effect its proved a new potential therapeutic approach which directly involved in JAK inhibition [8].

Noggin is also a potential inhibitor of bone formation with small suturectomy sites, which is useful in avoiding post operative re-synostosis. Which may be useful an adjunct to traditional surgical intervention to treat the craniosynostosis [9].

Moreover, FGFR signaling and its cross talk with tyrosine kinase and immunoglobulin's i, ii, iii, iv controlling skeletal cell fate. Pharmacologically we should target to correct the deformity of cell phenotype [10].

Material and Methods

Successful gene therapy requires standardized techniques. Retroviruses are a class of viruses that having the ability to produce double-stranded DNA copies from their RNA genomes. Selected Copies of its Genome can be made to integrate into target chromosomes of host cells. Adenoviruses are another class of viruses with the capability of inserting their genetic material at a specific site of chromosome. A similarly Herpes simplex virus infects a particular cell type, neurons. HSV type I is very common pathogen, which causes cold sores. However, direct introduction of therapeutic DNA into target cells, is easier than others. Its application only in selected tissues requires large amounts of DNA. Non-viral approach involves the creation of an artificial lipid sphere with an aqueous core. Liposomes carry the therapeutic DNA and are capable to transmitting the DNA through the specific target cells membrane.

The process of the inserting therapeutic DNA into target cells by chemically linking the DNA to a molecule that binds to special receptors. When bound to receptors, the therapeutic DNA constructs are engulfed by cell membrane and transported inside the target cell. The difficulty arises in delivering these larger molecules to the nucleus of the target cell.

Results

Microarray technology reports suggested that the data confined globally in gene expression between regional dura mater underline fusing with patent sutures. Which play a major role in cranial suture biology [11].

Moreover, various cytokine signaling pathways are investigated and promising for the future development of potential alternative therapy to solve the disease like craniosynostosis and craniofacial deformity

Sl.No	Disorder	Enzyme	Inheritance	Clinical Manifestations
1	Actalasia	Catalase	AR	May present as oral gangrene.
2	Albinism	Tyrosinase	AR X-Linked	Lack of pigment in skin, hair and eyes.
3	Alkaptonuria	Homogentisic acid oxidase	AR	Arthritis
4	Cystinuria	Not Known	AR	Renal stores, aminoaciduria
5	Galactosaemia	Galactose-1-phosphate uridyl transferase	AR	Mental retardation, contract, cirrhosis
6	Gaucher's Diseases	Glucocerebrosidase	AR	Hepatosplenomegaly, Thrombocytopenia and anaemia
7	G-6-PD Deficiency	Glucose-6-phosphate dehydrogenase	X-Linked	Haemolysis in response to some drugs.
8	Hunters syndrome	Sulphoid duronate sulphatase	XR	Haepatosplenomegaly, mental retardation, skeletal abnormalities.
9	Isoniazid inactivations	N-acetyl transferase	AR	Neurological Problems.
10	Niemann-Pick	Sphingomyelinase	AR	CNS damaged, cherry red
	Disease			spot on macula and hepatospelanomegaly
11	Phenyl ketonuria	Phenyl alanine hydroxylase	AR	Microcephaly, mental retardation
12	Prophyria (Acute intermittent)	More hepatic ALA synthestase	AR	Acute abdominal pain episode, neurological problems, excessive excreation of amino-levu-linic acid (ALA) in urine.
13	Tay-Sachs Diseases	Hexosaminidase-A	AR	Convulsions, Mentalretardation, Blindness
14	Vitamin-D resistant rickets	Renal defect in phosphate reabsorption	XD	Rickets
15	Wilson's Diseases	Not Known	AR	Cirrhosis of liver, kayser- Flesher ring in cornea, neurological problems.
16	Hurler's Syndrome	α- Iduronidase	AR	Same as above, in addition there is corneal clouding.
17	Achondroplasia	tyrosine kinase	AD	Skeletal Deformity
18	Cystic fibrosis	Proteincysticfibrosis transmembrane conductor regulator	AR	Critically lungs, pancreas liver and intestine.
19	Chronic Mylogenus Leukemia	White blood cells	CT	Increased and unregulated growth of predominantly myeloid cells in the bone marrow.
20	Parkinson Diseases	-Synuclein protein	FM	Tremor at rest, stiffness, slowing of movement and postural instability.

*AR- Autosomal Recessive; CT-Chromosomal Translocation; FM-Familial

Table 1: Inborn errors of metabolism important examples.

[12]. Microinjection techniques are developed newly cell membrane and intracellular dyes. The number of (RNA and DNA viral) constructs are delivering the genes to enhancing the solution of cell fate maps, cell lineage activities which are more approachable for human diseases.

TGF-beta also playing a role of different is forms to produce craniosynostosis the specific receptors, signaling pathways, animal models, expressions also helpful for normal and pathological sutures [13].

For improving collaborating with different clinical manifestations, centers, standardization, data collection and addressed should be the special priorities. We should focus team approach to solve this problem in near future for public health research and education for craniosynostosis/birth defects and other diseases [14].

Genetic counseling

Genetic counseling is a process to assist the parents and family. They should understand the nature of genetic disorder and its risk of transmission to subsequent siblings. The available options for prenatal diagnosis and medical termination of pregnancy are as follows.

Gene therapy in medical informatics

Gene therapy with replacement of abnormal gene is curative. But it is still in experimental stage. GT has been tried in patients with Adenosine Deaminase Deficiency (ADA) Duchenne Muscular Dystrophy (DMD), familial hypercholesterolemia and certain cancers. The aim is to replace the deactivate gene with the normal gene. This is done by using a viral or non-viral vector for introducing the normal functioning gene.

Discussion

Many inherited metabolic diseases will not require complete restoration of gene function for correcting important aspects of the disease phenotype. e.g. Parkinsonism, phenylketouria and other diseases. Pseudogene and transgenic expression are adequate (Table 1). In general view, both the significance of the role for somatic gene therapy and molecular mechanisms for its implementation have evolved dramatically now days (Table 2). Particularly, candidates have expanded from just single-gene disorders to include Cancer, AIDS, Birth Defects, Craniofacial deformities and atherosclerosis. Distinguished with another area of change is the expansion of the delivery system, which began retroviral vectors but now includes vectors based on adenovirus, Adeno-Associated Viruses (AAV), herpes virus, vaccine, and other agents are documented Non-viral systems such as liposomes, DNA-protein conjugates, and DNA-Protein-defective virus conjugates are also promising. Retroviral vectors have the major advantage that they integrate with the foreign DNA and permanently alter the recipient cell; But they have two major disadvantages namely requirement for dividing cells and they need to provide low-titer virus, which is relatively impractical for most *in vivo* approaches. In-contrast, adenovirus vectors can be offered as high titer and they have the ability to effect large number of cells in-vivo, but there is concern about toxic effects on infected cells, and the therapeutic effects is only transient. Both in-vivo and in-vitro results have been good. Gene therapy has so far been reported to be useful in few genetic disorders, including ADA deficiency and hypercholesterolemia. Many trials have been approved for many malignancies, AIDS, Cystic fibrosis, Gauchers Diseases, A Craniofacial defects (Table 3). As per the development of recent advancement like microarray, next generation sequencing, SSCP, SNPs, DDGE, RFLP, Bloting, karyotyping, ARMS, Direct sequencing, VNTRS, microsatellites and other molecular techniques are more helpful to developed these therapeutics.

In the present scenario it seems that this new form of therapy is far from routine bed side clinical application.

GT for single-gene disorders like syndromic and non-syndromic craniosynostosis diseases are still not well documented or progressed. Though it is highly promising and very serious threaten in near future. Researcher, Scientist, Clinicians, paramedic, Tissue Engineers should focus on developing therapy for these patients. Government and funding agencies should take necessary action for achieving this goal. Even suicide gene therapy is one of the most promising therapies to treat mesothelioma. A protein-producing gene is introduced that converts a non-toxic drug into one that can kill cancer cells. Cytokines are proteins that control and direct our immune response. It helps immune systems to an attack against cancer cells. Controlled gene expression, getting genes to their proper targets, preventing destruction of the gene, delivery methods, condition of the host and host immune response are some of the challenges facing genetherapy. Moreover, viruses, viral delivery methods, Liposome delivery, and targeted gene delivery in cellular level in-vitro and in-vivo need to be improved.

Side effects

Gene therapy and potential complications are including the long term effects of the treatment remain unknown. Though it has not yet

Sl.N o	Disease	Causes/Through	Approach
1	Genetic Defect	ADA-SCID	GT
2	Defective Gene	M-RNA	NGT
3	Thalassaemia	Blood Disorder	Copen-rnicus therapeutics
4	Cystic fibrosis		
5	Some Cancers		
6	Sickle-Cell Diseases	HbF	Hydroxyurea/ HbF
7	Hereditary Diseases	Hematopoietic Stem Cells	GT
8	Severe combined immune deficiency or "bubble boy" Diseases	Hematopoietic Stem Cells	GT
9	Parkinson Diseases	Polyethylene glycol	IG
10	Huntington's Diseases	RNA Interference/Gene silencing	GT
11	Coronary artery Diseases	Cardiomyocytes	HHPDT

*GT-Gene Therapy; NGT-New Gene Therapy; IGT-Insertion Gene Therapy; HbF-Fetal Hemoglobin; HHPDT-Human HGF plasmid DNA Therapy

Table 2: Major developments in gene therapy.

Sl. No	Diseases	Chromosomal location	Approach
1	Di George Syndrome	Di George: 22q	NGT
2	Velocardio facial Syndrome	Velocardio facial: 22q	NGT
3	Vander Woude Syndrome	Vander Woude: 1q	NGT
4	Treacher Collins Syndrome	Treacher Collins: 5q	NGT
5	Saethre-Chotzen Syndrome	Saethre-Chotzen: 7p	NGT
6	Cleidocranial Dysplasia	Cleidocranial Dysplasia: 6p	NGT
7	Holoprosencephaly	Holoprosencephaly: 2p,7q	NGT
8	Adelaide Type	Adelaide Type CS:4p	NGT
9	Greig Syndrome	Greig: 7p, GLI-3	NGT
10	Stickler Syndrome	Stickler: 12q,COL2A1, 6p, COL11A2	NGT
11	Waardeburg Syndrome	Waardeburg I: 2q, PAX3, 11:3p, MITF	NGT
12	Boston Types CS	Boston Types CS: 5q, MSX2	NGT
13	Crouzon Syndrome	Crouzon: 10q, FGFR2	NGT
14	Pfeiffer Syndrome	Pfeiffer: 8p, FGFR1, 10q, FGFR2	NGT
15	Jackson-Weissman Syndrome	Jackson-Weiss: 10q, FGFR2	NGT
16	Achondroplasia	Achondroplasia: 4p, FGFR3	NGT
17	Thanatophoric Dysplasia	Thanatophoric Dysplasia: 4p, FGFR3	NGT
18	Duchenne's Muscular Dystrophy	DMD Gene: Exon-51 deletion	Antisense oligonucleotide PROO51
19	Edward Syndrome	Edward: trisomy-18	NGT
20	Down Syndrome	Down: trisomy-21	NGT

*NGT-New Gene Therapy

Table 3: Most Promising and gene therapy need to be improved according to our experience in craniofacial deformities or craniosynostosis syndromes.

been observed researchers have raised concern that healthy cells may also become infected by the modified viruses, which could possibly cause new diseases or lead to carcinogenesis.

Conclusion

It is hoped that molecular genetics techniques will be useful not only for diagnosis of disease, but for treatment as well. The normal gene may be introduced directly into the defective body organ i.e. *in vivo* or more often the process is achieved *in vitro* followed by its introduction into the patient. Another obstacle to genetherapy is the high cost involved. GT should always be monitored and instituted at centers with sufficient experience and expertise. In the absences of definite treatment modalities it appropriate to create awareness among clinicians regarding counseling and preventive strategies. Newer tools in medical informatics to provide e-learning, such as simulation, animation, and media may be exploited to provide better treatment and to foster future research.

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