6 Principles of Therapeutics

Maria Descartes · Edward J. Lose

The medical treatment of genetic disease is now at the stage that the field of infectious disease was at after Koch's postulates were formulated. The causes of disease and malformations due to changes in the genetic sequence or outside of the genetic code (epigenetic modification) have been rapidly catalogued over the last few decades. Treatment of genetic disease has been so far mainly palliative in nature and generally addresses the pleiotropic manifestations. The complications of many genetic disorders are increasingly amenable to some form of medical or surgical treatment. Accomplishing a more disease-specific treatment of genetic disorders has remained an elusive goal, yet the growing number of therapeutic responses shows that progress has been made in controlling and reducing associated symptoms. The foundation of future-directed therapy for genetic disorders is based on the understanding of genetic disease at the molecular level.

Systemic Therapy

Many genetic syndromes exhibit organ or multisystem malformations. The surgical and medical treatment of these complications is long established, and results in prolonged survival with improved quality of life. These treatments include congenital heart disease repair, orthopedic surgery for skeletal malformations, neurosurgery for hydrocephalus, and many more. Although successful, these interventions are not unique to genetic disease and do not specifically address the underlying pathology (*Fig. 6.1*).

Organ Transplantation

Organ transplantation involves replacing the malfunctioning organ along with the relevant somatic stem cells and differentiated cells. Liver transplantation is used for a number of metabolic disorders, including urea cycle disorders, organic acidurias, homozygous familial hypercholesterolemia, and severe forms of glycogen storage disease. The liver disease associated with cystic fibrosis and α-1-antitrypsin deficiency may also be treated with liver transplantation. Somatic stem cells are capable of self-renewal and differentiation into different cell types, making them excellent candidates for cellular therapy. Liver repopulation by transplanted hepatocytes is a promising approach.

Hematopoietic Cell Transplantation

Transplantation of hematopoietic (multipotent) stem cells from bone marrow (HCT) has been used for the past 2 decades in immunodeficiency, lysosomal, and peroxisomal disorders. The rationale of this treatment is based on providing the missing enzyme through donor cells within and outside the blood compartment. The great majority of transplants have been performed in patients with Hurler syndrome (MPSI), Hunter syndrome (MPSII), Sanfilippo syndrome (MPSIII), Maroteaux–Lamy syndrome (MPSVI), X-linked adrenoleukodystrophy, metachromatic leukodystrophy, globoic-ceroid leukodystrophy (including Krabbe disease), and others (Pelizaeus–Merzbacher, Zellweger syndrome, and vanishing white matter disease).

Allogenic hematopoietic cell transplantation (HCT) is the only treatment with curative potential for sickle cell disease and beta-thalassemia. Successful treatment relies on a permanently viable engraftment as opposed to a transient engraftment. Availability of matched donor, graft failure, and transplantation-related mortality remain limiting factors.

Unrelated cord blood (UCB) transplantation is the utilization of umbilical cord blood as a stem cell source. The use of cord blood has several advantages over bone marrow as a source of stem cells. The recipients are more tolerant of histoincompatible blood than other donor cells. Placental cord blood is widely available and transplantation from unrelated donors appears to be as effective as from a matched donor, at least for Hurler syndrome and neonatal Krabbe disease. Still investigational is the use of mesenchymal stem cells (MSCs) infusions. Mesenchymal stem cells are pluripotent cells that have the potential of differentiating into various cells of meshencymal origin: osteoblast, chondrocytes, adipocytes, and astrocytes.

In mice, inducible pluripotent stem cells (iPS cells) have been created from skin fibroblasts and effectively transformed into hepatocytes. In the model utilized, the

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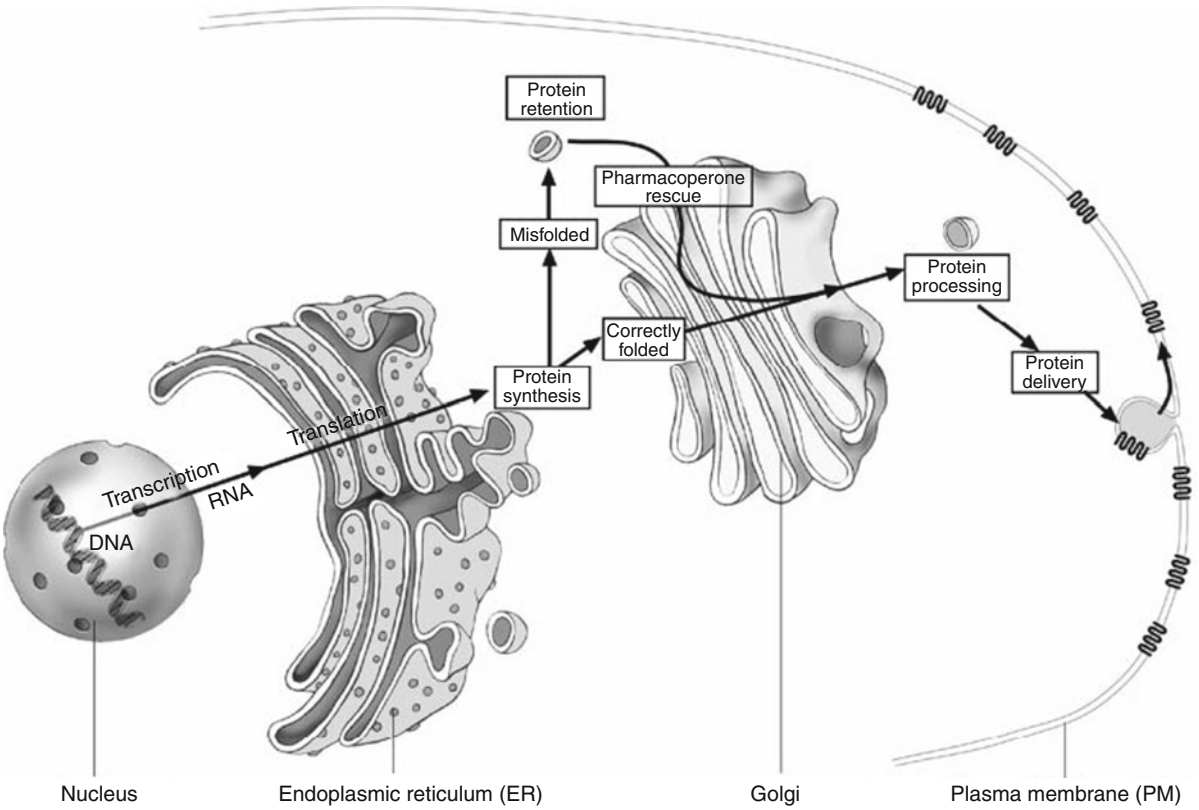


Figure 6.1
Various levels of treatment for genetic diseases (Pharmacol Rev 2007 59:225–250

subject mice were homozygous for fumarylacetoacetate hydrolase deficiency (hereditary tyrosinemia). The FAH -/- cells died and the iPS cells effectively replaced the entire liver. Human iPS cells have been generated and considerations for trials include the following conditions: α-1-antitrypsin deficiency, familial hypercholesterolemia, glycogen storage disease type 1 (von Gierke disease), hereditary tyrosinemia, and Crigler–Najjar syndrome.

Therapy at the Extracellular Level

Metabolic Pathway Modification

Inborn errors of metabolism are the archetype of genetic disorders. Newborn screening programs are the most widespread genetic tests performed. These programs are effective in modifying or preventing complications because early therapy is often easily implemented. Treatment is targeted at restricting dietary intake of the substrates early in the metabolic pathway, increasing excretion of toxic metabolites, replacing deficient substances, and altering the primary metabolic rate. To achieve metabolic balance and stabilization of symptoms, these strategies are used individually or in combination.

Dietary therapy is a long-established and effective method of managing genetic disorders (*Table 6.1*). Dietary modification has been used successfully in aminoacidopathies, urea cycle disorders, and diseases of carbohydrate metabolism. Dietary restriction is usually a lifetime commitment and can be imposing to the family and the patient. Total protein restriction is necessary and sometimes severe for disorders of amino acid catabolism and the urea cycle. This must be balanced by supplying essential substrates and cofactors to allow for growth and development. Sugar restriction for disorders of carbohydrate metabolism can be as simple as limiting lactose consumption in galactosemia or as difficult as limiting total glucose consumption in pyruvate dehydrogenase deficiency. Patients with fatty acid oxidation defects usually require acute management only and are otherwise allowed a relatively unrestricted diet.

Table 6.1
Disorders that respond to dietary therapy

Disorder	Restriction	Supplementation
Aminoacidopathies		
Phenylketonuria	Phenylalanine	Tetrahydrobiopterin for responsive patients
	Total protein	
Tyrosinemia Tyrosenemia I? or tyrosemia I and II? Tyrosemia I is usually responsive with NTBC (nitisinone) also known as: 2-(2-nitro-4-trifluoro-methylbenzoyl)-1,3 cyclohexanedione	Phenylalanine	
	Tyrosine	
Homocystinuria	Methionine	Pyridoxine for responsive types, betaine, folate, hydroxycobalamin
	Total protein	
Carbohydrate metabolism defects		
Pyruvate carboxylase deficiency	High carbohydrate and high protein diet to avoid activation of gluconeogenesis	Citrate supplementation, biotin, aspartic acid, triheptanoin
		Thiamine, carnitine, lipoic acid
Pyruvate dehydrogenase deficiency	Glucose/Carbohydrates	Fat intake
	Branched chain amino acids	Thiamine, lipoic acid
		Cornstarch
		Protein
Hereditary fructose intolerance	Fructose, sucrose	
	Sorbitol	
Galactosemia	Galactose, lactose	
Fatty acid oxidation defects		
Short chain acyldehydrogenase deficiency	None	Carnitine
Medium chain acyldehydrogenase deficiency	None	Carnitine
Long chain acyldehydrogenase deficiency	None	MCT oil and low fat diet
Trifunctional protein deficiency	Long chain fats	MCT oil, carnitine, DHA
Organic acidemias		
Branched chain organic acidurias		
Maple syrup urine disease	Isoleucine, leucine, valine	
Isovaleric acidemia	Leucine	Levocarnitine and glycine
Propionic acidemia	Isoleucine, valine, methionine, threonine	Levocarnitine and biotin
Methylmalonic acidemia	Isoleucine, valine, methionine, threonine	Folate, betaine, and levocarnitine Cyanocobalamin for cobalamin responsive patients
Glutaric Acidemia Type 1	Lysine, hydroxylysine, tryptophan	Levocarnitine, riboflavin
	Tryptophan	
Urea cycle defects		
In general	Total protein	
N-Acetylglutamate synthetase deficiency		Carbamylglutamate

Table 6.1 (Continued)

Disorder	Restriction	Supplementation
Carbamoylphosphate synthetase deficiency		
Ornithine transcarbamylase deficiency		Arginine, citrulline
		Sodium benzoate
		Sodium phenylacetate
Citrullinemia		Arginine
Arginosuccinic aciduria		Arginine
Arginase deficiency		

Limited understanding of the metabolic pathway and interactions involved in disease progression still poses a barrier to effective treatment. Despite a reduction in the occurrence of cataracts and mental retardation with the institution of lactose restriction in galactosemia patients, 81% of females with this disorder experience premature ovarian failure and 56% of males and females have delayed vocabulary and articulation milestones. Additionally, intercurrent illness and stress may provoke a crisis in otherwise stable patients. Rapid response with dietary modifications and intravenous therapy can avert deterioration in many cases.

In a number of metabolic disorders, the efficiency of the defective enzyme or an alternative pathway can be enhanced by the administration of large amounts of the vitamin cofactor. The administration of cofactor may overcome reduced affinity of the mutant enzyme for the cofactor or stabilize the enzyme. Nonresponsive patients generally have a mutation that result no residual enzyme activity.

Phenylketonuria (PKU) is the first genetic disorder for which a screening process was introduced in the 1960s. PKU is traditionally treated with a phenylalanine-restricted diet. Tetrahydrobiopterin is a cofactor that binds to the affected enzyme, phenylalanine hydroxylase. A tetrahydrobiopterin analog, Sapropterin, is the first non-dietary treatment for patients with phenylketonuria (PKU). Sapropterin dihydrochloride (Kuvan®) is a synthetic formulation of the active 6R-isomer of tetrahydrobiopterin, a naturally occurring cofactor of phenylalanine hydroxylase. The mechanism of action appears to be related to its effect in augmenting and stabilizing abnormal phenylalanine hydroxylase molecules, thus increasing the clearance of phenylalanine from the body. It is approved to treat hyperphenylalaninemia in patients ages 4 or more years with tetrahydrobiopterin-responsive phenylketonuria.

For disorders characterized by accumulation of toxic metabolites, excretion of the offending substance is the preferred therapeutic method. Additionally, the offending substance can be reduced by activation of alternative pathways, inhibition of normal feedback inhibition, and pharmacologic agents used to promote elimination.

Nitrogen scavengers such as sodium benzoate, phenylbutyrate, or phenylacetate are utilized in patients with urea cycle disorders. They promote nitrogen elimination and avoid toxic accumulation of the ammonium ion. Adjunct clearance mechanisms are used in disorders characterized by failure of normal metabolic clearance to excrete excess amounts of substrate. Chelation therapy with penicillamine and trienetine are used to increase copper excretion in Wilson disease. Serial phlebotomy is the treatment of choice in hemochromatosis to remove the excess iron.

Hereditary tyrosinemia type I is due to a deficiency of fumarylacetoacetase, which leads to the accumulation of fumarylacetoacetate and maleylacetoacetate. Both chemicals are then metabolized via an alternative pathway to succinylacetone – the metabolite responsible for many of the neurological symptoms of this disorder. In addition to dietary restriction of tyrosine and phenylalanine, 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione (NTBC) is used to divert the tyrosine catabolism pathway upstream of homogentisic acid toward a normally dormant urinary excretion pathway. This reduces the levels of fumarylacetoacetate, maleylacetoacetate, and succinylacetone, thus reducing or averting the hepatic complications of the syndrome such as cirrhosis and hepatocellular carcinoma. Allopurinol has been used similarly in disorders leading to hyperuricemia like Lesch–Nyhan syndrome, and hematin is used in acute intermittent porphyria to decrease the activity of δ-aminolevulinic acid synthetase, thereby reducing porphyrin production.

Replacement of a deficient substrate can also be an effective treatment. Smith–Lemli–Opitz syndrome is a disorder of cholesterol biosynthesis. Cholesterol supplementation has provided some benefit to patients with this

disorder. Large doses of carnitine are effective in carnitine transport defects.

Protein Replacement Therapies

Protein replacement therapy refers to production, purification, and administration of the missing protein to the patient. This therapy is used in several hereditary disorders, including cystic fibrosis, hereditary angioedema, coagulation disorders, α-1-antitrypsin deficiency, immunoglobulin deficiencies, endocrine disorders, and lysosomal storage diseases (Table 6.2).

Enzyme replacement therapy is effective in the nonneurological symptoms of mucopolysaccharidosis types I, II, IV, and VI, Pompe, and Niemann–Pick B (not approved), but has not yet proven to be beneficial in storage diseases that primarily affect the central nervous system, since the replacement enzymes do not efficiently cross the blood–brain barrier.

Metabolic inhibition

Another approach to the therapy of lysosomal storage disorders due to defects in enzymes involved in glycosphingolipid degradation (including Gaucher disease types 1, 2, and 3, Fabry disease, Tay–Sachs disease, Sandhoff disease, and G_{M1} gangliosidosis) is substrate reduction therapy (SRT). SRT is a biochemical approach that makes use of substrates that inhibit and therefore reduce the rate of macromolecule synthesis. Miglustat (*N*-butyl-deoxynojirimycin/NB-DNJ) inhibits the initial committed step in glycosphingolipid synthesis, therefore reducing the substrate of the missing enzyme. For example, children with Tay–Sachs disease accumulate high levels of G_{M2} ganglioside in brain cells, which causes cell death. Decreasing the synthesis of G_{M2} would presumably decrease cell death and moderate the course of the disease. Miglustat has been approved in Europe and the United States for the treatment of the mild form of Gaucher type 1 and in Europe for the treatment of Neiman–Pick type C. Miglustat is in clinical trials in adults and children with juvenile G_{M2}, Tay–Sachs, and Sandhoff disease, and in young children under the age of 2 with Tay–Sachs and Sandhoff disease. Some affected individuals or parents of those affected do explore with their physicians the option of using this treatment on an "off-label" basis.

Treatment of the Molecular Mechanism

Marfan syndrome affects 1 in 5,000 individuals and is a systemic connective tissue disorder caused by mutations in the gene for fibrillin-1. It was originally thought that the clinical manifestations of Marfan syndrome were solely

Table 6.2
Protein replacement therapy

Disease	Protein	Trade name
Cystic fibrosis	Digestive enzymes	Multiple
Hereditary angioedema	C1 inhibitor	Cinryze
Coagulation disorders		
For example, Hemophilia A	Factor VIII	
α-1-Antitrypsin deficiency	α-1-Antitrypsin	Prolastin
Immunoglobulin deficiencies	Intravenous immunoglobulin	IVIG
Gaucher disease	Glucosidase	Imiglucerase (Cerezyme), velalglucerase (VPIV)
Fabry disease	α-Galactosidase	Agalsidase-beta (Fabrazyme, Replagal)
Type 1 Hurler, Scheie, Hurler-Scheie	α-L-Iduronidase	Aldurazyme
Type 2 Hunter	Iduronate-2-sulfatase	Idurulfase (Elaprase)
Type 4 Morquio		
A	Galactosamine-6-sulfatase	
B	α-Galactosidase	
Type 6 Maroteaux–Lamy	*N*-Acetylhexosamine-4-sulfatase	Galsulfase (Naglazyme)
Pompe	Acid α-glucosidase	Alglucosidase alfa (Myozyme, Lumizyme)

the result of the production of abnormal fibrillin-1, resulting in changes in the structural integrity of the affected organs. Recent molecular and animal studies have shown that it is a developmental abnormality due to altered transforming growth factor-beta signaling. In the mouse model of Marfan syndrome, the use of an antagonist (Losartan) of the transforming growth factor beta-angiotensin II signaling pathway has been shown to prevent and reverse manifestations of the disease, including aortic root dilation. Losartan is currently undergoing clinical trials.

Therapy at the Intracellular Level

Protein Enhancement Therapy: Chaperones

Inherited mutations can disrupt native protein folding, thereby producing proteins with an abnormal three-dimensional conformation. These misfolded proteins, which may otherwise be sufficiently active, are consequently retained and degraded in the endoplasmic reticulum-associated degradation pathways. The most widely known of these is the ΔF508 mutation in the cystic fibrosis transmembrane conductance regulator.

Among the newest therapeutic modalities is the utilization of low-molecular-weight compounds known as chaperones to stabilize the functional form or three-dimensional shape of a mutated protein in the endoplasmic reticulum. The binding of the chaperone molecule allows the protein to fold into its correct three-dimensional conformation and be properly trafficked through the endoplasmic reticulum. The protein then resumes its proper path to the correct site in the cell. Pharmacological chaperone therapy is in early stage clinical trials for lysosomal storage diseases: Fabry disease utilizing 1-deoxygalactonojirimycin which is a potent inhibitor of α-galactosidase. The inhibitor is given in low quantities which paradoxically enhances the intracellular activity of the residual enzyme.

Transcriptional Therapy

Increasing knowledge of gene expression will allow another potential tool for therapy, transcriptional therapy. Transcriptional therapy is aimed at modulating, modifying, or reactivating genes. These types of modifications of the genome include: reducing the expression of a dominant mutant gene product by RNA interference (RNAi), increasing the expression of a gene that can compensate for the effect of the mutation at another locus, and increasing the amount of messenger RNA (mRNA) of silent or poorly expressed genes.

Hereditary angioedema (AD inheritance) is a potentially fatal disorder due to a mutation in complement 1 (C1) esterase inhibitor. Affected individuals have unpredictable episodes of submucosal and subcutaneous edema. If the upper respiratory tract is involved, this disease can be fatal. Danazol, an attenuated androgen, is used in the long-term prophylactic treatment of this condition, by increasing the abundance of C1 inhibitor mRNA. Current treatment for sickle cell disease includes hydroxyurea, which results in an increased production of fetal hemoglobin. A promising strategy in the treatment of hemoglobinopathies such as sickle cell disease and β-thalassemia is the use of drugs that induce DNA hypomethylation. These drugs increase the abundance of fetal hemoglobin (HbF, $\alpha 2\gamma 2$). HbF is normally underexpressed in adults (<1% of total hemoglobin) as a result of normal globin switching in infancy. The underexpression of the HbF is in part due to methylation of the promoter of the γ-globin gene. This methylation can be inhibited by cytidine analogs, such as decitabine (5-aza-2′deoxycytidine).

Conditions that are the result of pathologically silenced (hypermethylated) genes could theoretically be treated with drugs that cause DNA demethylation, thereby reactivating normal transcription. Fragile X syndrome is the result of pathological silencing of the FMR1 gene (Xq27.3) due to an abnormal trinucleotide repeat (CGG) expansion near the FMR1 promoter. The nucleotide analog 5-azadeoxycytidine (5-azadC) is an irreversible inhibitor of DNA methyltransferases, which predominantly methylate CpG dinucleotides in the human genome. In vitro treatment of fragile X cells with 5-azadC lead to reactivation of FMR1 transcription. Drugs that target other forms of gene inactivation are also being investigated (e.g., histone acetylation). Other candidates are conditions that result from deletion or uniparental disomy of an imprinted gene.

Pathological changes can result from the production of a gene product that is toxic to the cell, as in Huntington disease. Additionally, an abnormal collagen chain produces a structurally weakened collagen triple helix in osteogenesis imperfecta. Diminishing the amount of the mutant protein without altering the production of the normal allele may ameliorate the phenotype. This goal might be reached by creating double-stranded RNA molecules that are degraded prior to translation. RNA interference (RNAi) technology utilizes RNAi directed against the mutant mRNA, which inactivates the specific mRNA transcribed

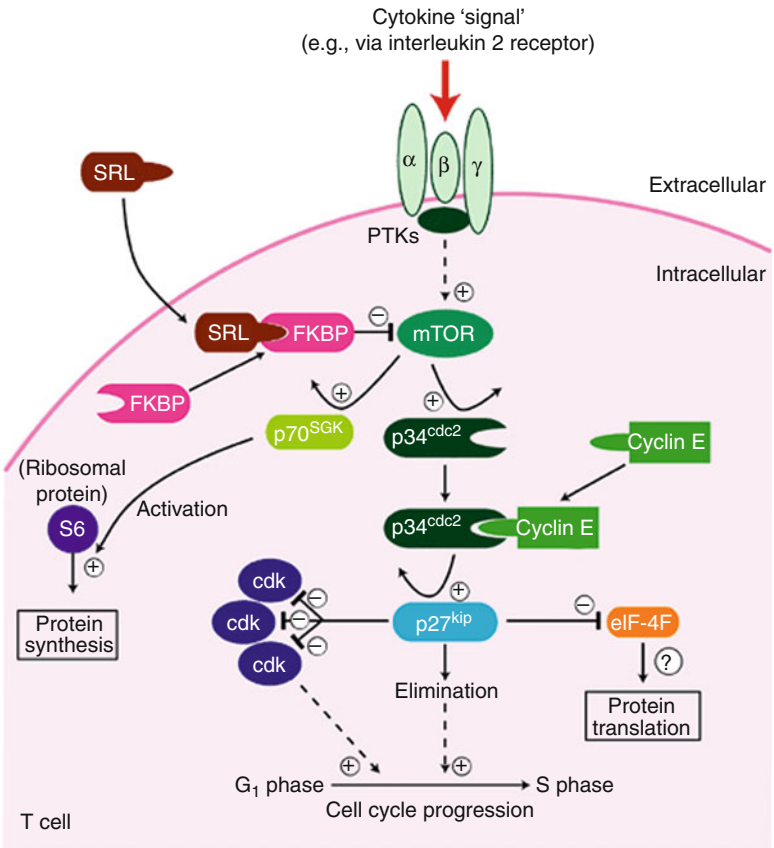
by the mutant allele while not binding and inactivating the mRNA transcribed by the normal allele.

Translational Therapy: Stop-Codon Read-Through Drugs

One-third of inherited diseases are the result of mutations that create premature termination codons. These include cystic fibrosis, muscular dystrophy, hemophilia, familial hypercholesterolemia, lysosomal storage disorders, and several types of cancer. Aminoglycosides (gentamicin) can suppress premature translational termination induced by nonsense mutations and prompt ribosomes to generate full-length proteins. In preclinical and pilot clinical studies, this therapeutic approach shows promise in reducing or eliminating the phenotype by promoting protein synthesis. The challenge ahead is to maximize efficacy and minimize side effects.

Pathway Modification

Several genetic syndromes are the result of mutations in known pathways that control transcription. Sirolimus (rapamycin) is an immunosuppressant medication with activity in the mTOR pathway (see *Fig. 6.2*). This results in blocking of cytokine-initiated signaling. The mTOR pathway is affected in several syndromes such as tuberous sclerosis complex (TSC) and the Ras pathway syndromes – neurofibromatosis, Noonan syndrome, cardiofaciocutaneous syndrome, Costello syndrome, and LEOPARD syndrome. These syndromes are marked by the constituitive activation of ras-signaling the mTOR



Mechanism of action of sirolimus (rapamycin)
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Figure 6.2
Mechanism of action of sirolimus (rapamycin) (Expert Reviews in Molecular Medicine ©2000 Cambridge University Press)

pathway. Rapamycin and other mTOR inhibitors are currently in clinical trials to gauge effectiveness in preventing the formation and growth of neurofibromas in NF1 and various manifestations of TSC.

Cell Replacement Therapy

The isolation and utilization of pluripotent and totipotent embryonic stem cells has previously been restricted to the creation of recombinant animal models of human disease. Recently, these stem cells have been stimulated to follow known differentiation pathways which yield specific cell types. These manufactured cells might then correct human disease resulting from the lack of secreted products, or urged to differentiate in situ to replace the diseased cells. There are currently multiple entries in ClinicalTrials.gov regarding stem cell research. Some examples of diseases are listed in *Table 6.3*.

Gene Therapy

In principle, this approach seems straightforward. It is possible now to create mutant animal phenotypes and to correct them utilizing recombinant technology. The application to humans is problematic. One cannot reverse the embryologic development of a human fetus; therefore, altering a structural defect is not currently possible. The diseases considered for gene therapy are thus restricted to those associated with continuously replicating cells such as hematopoietic cells and epithelial cells, or enzyme defects in accessible cells. The mechanism of molecular modification utilizes both random insertion of a correct genetic sequence into the genome and homologous recombination to correct the specific mutation. For each specific combination of vector, transgene and target tissue one or two of the following problems predominate: gene silencing, insertional mutagenesis, phenotoxycity, immunotoxicity, horizontal transmission of the donated DNA, vertical transmission (Mingozazi F, High KA. Therapeutic in vivo gene transfer for genetic disease using AAV: progress and challenges).

The vectors utilized to deliver the DNA therapy must be taken up by mammalian cells and ultimately the DNA must travel to the nucleus and become incorporated either by insertion or homologous recombination. Eukaryotic viruses such as adeno-associated viruses (AAV) have been most commonly utilized. The mammalian cells are efficient in the uptake of AAV, and the therapeutic DNA sequence is effectively delivered to the nucleus where recombination or insertion takes place.

Table 6.3
Conditions amenable to stem cell therapy

Disease	Organ	Therapy	Phase	Sponsor
Multiple sclerosis	Brain	PBSCT	3	Northwestern University
Myasthenia gravis	Brain	Hematopoietic stem cells	1	Northwestern University
Pressure sores	Skin	Hematopoietic stem cells	1	University Hospital Basel, Switzerland
Coronary artery disease	Heart	Cardiac stem cells	1	University of Louisville
Congestive heart failure	Heart	Hematopoietic stem cells	3	Johann Wolfgang Goethe University Hospitals
Brachial plexus denervation	Arm	Hematopoietic stem cells	3	Leiden University Medical Center

Table 6.4
Conditions amenable to DNA therapy

Disease	Organ	Therapy	Phase	Sponsor
Leber congenital amaurosis	Eye	rAAV2-hRPE65	1	Hadassah Medical Organization
Chronic granulomatous disease	Hematopoietic	Retroviral	0	NAIAD
Advanced malignant thyroid tumors	Thyroid	rAd-p53	4	Shenzhen SiBiono Genetech
Malignant glioma	Brain	ADV-TK	2	Huazhong University

If the desired effect is to suppress gene expression, then small inhibitory RNA strands (siRNA) can be used. The siRNA binds selectively to mRNA strands and the resulting double-stranded RNA is degraded by the cell prior to translation. The delivery systems for siRNA are numerous and summarized in a table. The siRNA incorporation is transient and does not yield a long-term solution.

Children with cystic fibrosis have temporarily incorporated exogenous DNA in their lungs utilizing an adenovirus vector, but the underlying stem cells were not transfected and the effect was transient. Another setback occurred with the death of a patient with OTC deficiency. It is believed that an immune response to the vector was the cause of death. The same results have occurred with a child who was being treated for severe combined immunodeficiency disorder (SCID). These issues have been addressed and therapies have been formulated for many disease states.

Newer trials are being undertaken with the hope of correcting mutations in target organs. There are currently many trials utilizing gene therapy. A few examples are listed in *Table 6.4*.

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