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The latest updates in genetic treatment

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(وَلَقَدْ آتَيْنَا دَاوُودَ وَسُلَيْمَانَ عِلْمًا وَقَالَا الْحَمْدُ لِلَّهِ الَّذِي فَضَّلَنَا عَلَى كَثِيرٍ مِنْ عِبَادِهِ الْمُؤْمِنِينَ)

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الاهداء

إلى أبي العطوف.... قدوتي، ومثلي الأعلى في الحياة؛ فهو من علَّمني كيف أعيش بكرامة وشموخ.

إلى أمي الحنونة..... لا أجد كلمات يمكن أن تمنحها حقها، فهي ملحمة الحب وفرحة العمر، ومثال التفاني والعطاء.

إلى إخوتي.... سندي وعضدي ومشاطري أفراحي وأحزاني.

إلى جميع من تلقَّيتُ منهم النصح والدعم من الأقارب والأصدقاء **أهديكم خلاصة جُهدي العلمي**

ألشكر والتقدير

الحمدلله ألذي هدانا وأعدنا وأمدنا والهمنا الصبر على المشاق ووفقنا لما نحن عليه

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والى كل من مد يد العون لي من قريب او بعيد

وقبل ان امضي اقدم اسمى ايات الشكر والامتنان والتقدير والمحبة

الى الذين مهدوا لي طريق العلم والمعرفة

الى جميع اساتذتي الافاضل

Introduction

The gene therapy approach can vary from delivering extra copies of a gene, through modifications of a genome using the properties of ribozymes or chimeraplasts, to injection of modified cells. For the treatment of genetic deficits, the ultimate goal would be the repair of the mutated gene in the target tissue(s). The techniques required for such an approach are emerging ,albeit slowly. Therefore, delivery of an extra copy of a normal gene in a specific vector remains the predominant approach

Moreover, this method finds wider applications in gene therapy relating to disorders other than heritable defects, e.g., malignancies, cardiovascular diseases and infections. The major and most intensive areas of research are: i) vectors and delivery methods, ii) regulation of transgene expression and iii) stability of expression. Targeting of the therapeutic gene is being accomplished by using viral vectors or non-viral delivery systems, either ex vivo or in vivo. The choice of vectors and delivery routes depends on the nature of the target cells and the required levels and stability of expression. Although there have been the first positive clinical results and significant technical achievements over the past 2 years, there are still obstacles to the development of effective clinical products and these remain largely unchanged. The most important barriers are the low levels and stability of expression and immune responses to vectors and/or gene products. The safety aspects of gene therapy have become painfully evident with the first death conclusively linked to gene therapy. The progress in AAV and lentiviral vectors, improved regulation of transgene expression and advances in stem cell technology are among the recent most exciting developments

Updates on gene therapy for diabetic retinopathy

Diabetic retinopathy (DR), a leading cause of visual impairment in the developed country, is characterized by vascular lesions and neuronal damage of the retina. Treatment options for this condition are currently limited. The advent of therapy targeting vascular endothelial growth factor (VEGF) demonstrated significant benefits to patients with DR. However, this treatment is limited by its short half-life and requirement for frequent invasive intravitreal injections. In addition, many patients failed to achieve clinically significant improvement in visual function. Gene therapy has the potential to provide an alternative treatment for DR with distinct advantages, such as longer therapeutic effect, less injection frequency, ability to intervene at disease onset, and potentially fewer side effects.

Recent Findings

Strategies for gene therapy in DR, stemming from the current understanding of the disease pathogenesis, focus on the inhibition of neovascularization and protection of neurovascular degeneration in the retina. Studies with promising results have mainly focussed on animal models due to efficacy and safety concerns, despite a number of successful preclinical studies using adeno-associated virus-mediated transduction to treat both vascular dysfunction and neuronal degeneration. With the optimization of delivery vectors, transgene regulation, and outcome measure, gene therapy will potentially become available for patients with DR.

Summary

This review provides an update on the current strategies utilized in DR gene therapy research. Several barriers to the clinical application of gene therapy for DR are highlighted, and future directions for this research are proposed.

Gene therapy for Parkinson's disease

The current mainstay treatment of Parkinson's disease (PD) consists of dopamine replacement therapy which, in addition to causing several side effects, does not delay disease progression. The field of gene therapy offers a potential means to improve current therapy. The present review gives an update of the present status of gene therapy for PD. Both non-disease and disease modifying transgenes have been tested for PD gene therapy in animal and human studies. Non-disease modifying treatments targeting dopamine or GABA synthesis have been successful and promising at improving PD symptomatology in randomized clinical studies, but substantial testing remains before these can be implemented in the standard clinical treatment repertoire. As for disease modifying targets that theoretically offer the possibility of slowing the progression of disease, several neurotrophic factors show encouraging results in preclinical models (eg, neurturin, GDNF, BDNF, CDNF, VEGF-A). However, so far, clinical trials have only tested neurturin, and, unfortunately, no trial has been able to meet its primary endpoint. Future clinical trials with neurotrophic factors clearly deserve to be conducted, considering the still enticing goal of actually slowing the disease process of PD. As alternative types of gene therapy, opto-and chemogenetics might also find future use in PD treatment

and novel genome-editing technology could also potentially be applied as individualized gene therapy for genetic types of PD.

Treatment for patient with genetic obesity

Obesity, defined by an excess of body fat impacting on health, is a complex disease resulting from the interaction between many genetic/epigenetic factors and environmental triggers. For some clinical situations with severe obesity, it has been possible to classify these obesity forms according to the molecular alterations. These include: (i) syndromic obesity, which associates severe early-onset obesity with neurodevelopmental disorders and/or polymalformative syndrome and (ii) non-syndromic monogenic obesity, due to gene variants most often located in the leptin-melanocortin pathway. In addition to severe obesity, patients affected by these diseases display complex somatic conditions, eventually including obesity comorbidities, neuropsychological and psychiatric disorders. These conditions render the clinical management of these patients particularly challenging. Patients' early diagnosis is critical to allow specialized and multidisciplinary care, with a necessary interaction between the health and social sectors. Up to now, the management of genetic obesity was only based, above all, on controlling the patient's environment, which involves limiting access to food, ensuring a reassuring daily eating environment that limits impulsiveness, and the practice of adapted, supported, and supervised physical activity. Bariatric surgery has also been undertaken in genetic obesity cases with uncertain outcomes. The context is rapidly changing, as new innovative therapies are currently being tested both for syndromic and monogenic forms of obesity. This review focuses on care management and new therapeutic opportunities in genetic obesity, including the use of the melanocortin 4 agonist,

setmelanotide. The results from ongoing trials will hopefully pave the way to a future precision medicine approach for genetic obesity.

Update on gene therapy for immunodeficiencies

Primary immune deficiencies (PID) are due to blood cell defects and can be treated with transplantation of normal hematopoietic stem cells (HSC) from another person (allogeneic). Gene therapy in which a patient's autologous HSC are genetically corrected represents an alternative treatment for patients with PID, which could avoid the immunologic risks of allogeneic HSCT and confer similar benefits. Recent clinical trials using gene therapy have led to immune restoration in patients with X-linked severe combined immune deficiency.

Gene therapy for sickle cell disease

Sickle cell disease (SCD) is one of the most common life-threatening monogenic diseases affecting millions of people worldwide. Allogenic hematopietic stem cell transplantation is the only known cure for the disease with high success rates, but the limited availability of matched sibling donors and the high risk of transplantation-related side effects force the scientific community to envision additional therapies. Ex vivo gene therapy through globin gene addition has been investigated extensively and is currently being tested in clinical trials that have.

Stroke genetics: a review and update

Stroke genetics includes several topics of clinical interest, including (1) molecular genetic variations affecting risk of monogenic stroke syndromes;(2) molecular genetic variations affecting risk of common stroke syndromes, sometimes with specific effects on risk of specific main types of stroke or subtypes of ischemic and hemorrhagic stroke;(3) genetics of conditions associated with stroke risk e.g. white matter hyperintensities, atrial fibrillation and hypertension;(4) hereditary causes of familial aggregation of stroke;(5) epigenetic impact on protein expression during acute brain injury;(6) genetic influence on stroke recovery; and (7) pharmacogenetics. Genetic research methods include candidate gene studies; Genome Wide Association Studies; family studies; RNA and protein analyses; and advanced computer-aided analytical methods to detect statistically significant associations. Several methods that could improve our knowledge of stroke genetics are being developed e.g.: Exome content analysis; Next-generation sequencing; Whole genome sequencing; and Epigenetics. During 2012-2014, several Single Nucleotide Polymorphisms (SNPs) have been related to common ischemic stroke risk. Certain SNPs have been associated with risk of specific ischemic stroke subtypes such as large vessel disease and cardiac embolism, particular subtypes of intracerebral hemorrhage (ICH), especially lobar ICH, and with prognosis after ICH. Large international studies on stroke recovery and exome content are ongoing. Advanced mathematical models have been used to study how several SNPs can act together and increase stroke risk burden. Such efforts require large numbers of patients and controls, which is achieved by co-operation in large international consortia such as the International Stroke Genetics Consortium. This overview includes an introduction to genetics, stroke genetics in general, and different genetic variations that may influence stroke risk. It presents some of the latest reports on stroke genetics published in high impact journals. The

role of pharmacogenetics, the current clinical situation, and future prospects will also be discussed.

The genetic and epigenetic alterations in human hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is one of the most frequent human malignancies worldwide with very poor prognosis. It is generally accepted that the progression of HCC is a long-term process with accumulation of multiple genetic and epigenetic alterations, which further lead to the activation of critical oncogenes or inactivation of tumor suppressor genes. HCC is characterized with multiple cancer hallmarks including their ability to proliferate, anti-apoptosis, invade, metastasis, as well as the emerging features such as stem cell properties and energy metabolic switch. The irreversible alterations at genetic level could be detected as early as in the pre-neoplastic stages and accumulate during cancer progression. Thus, they might account for the cancer initiating steps and further malignant transformation. In addition to genetic alterations, epigenetic alterations can affect the cancer transcriptome more extensively. Alterations in DNA methylation, histone modification, miRNAs, RNA editing, and lncRNAs might result in disrupted gene regulation networks and substantially contribute to HCC progression. In this review, the genetic and epigenetic alterations which significantly contribute to the malignant capabilities of HCC will be updated and summarized in detail. Further characterization of those critical molecular events might better elucidate the pathogenesis of HCC and provide novel therapeutic targets for treatment of this deadly disease.

An update on genetic basis of generalized pustular psoriasis

Generalized pustular psoriasis (GPP) is a rare and severe auto-inflammatory skin disease that is characterized by recurrent, acute onset, and generalized pustular eruptions on erythematous, inflamed skin. GPP is traditionally classified as a variant of psoriasis vulgaris, even though recent clinical, histological and genetic evidence suggests that it is a heterogeneous disease and requires a separate diagnosis. In recent years, variants of IL36RN, CARD14, AP1S3 and MPO genes have been identified as causative or contributing to genetic defects in a proportion of patients affected by GPP. These disease-related genes are involved in common inflammatory pathways, in particular in the IL-1/IL-36-chemokines-neutrophil pathogenic axis. At present, no standard therapeutic guidelines have been established for GPP management, and there is a profound need for novel efficacious treatments of GPP. Among them, biological agents antagonizing the IL-36 pathway are promising therapeutics. The aim of the present review is to provide the most recent updates on the genetics, genotype-phenotype correlation and pathological basis of GPP, as well as on biologic treatments available for GPP and relative clinical courses.

Effect of genetic polymorphisms on Alzheimer's disease treatment outcomes

Genetic variations in individuals may cause differences in the response to cholinesterase inhibitor drugs used in the treatment of Alzheimer's disease (AD). Through this review, we aimed to understand the potential relationship between genetic polymorphisms and treatment response in AD. We conducted a systematic review of the studies published from 2006 to 2018 that assessed the relationship between genetic polymorphisms and the pharmacotherapeutic outcomes of patients with AD. Via several possible mechanisms, genetic polymorphisms of many genes, including ABCA1, ApoE3, CYP2D6, CHAT, CHRNA7, and ESR1, appear to have strong correlations with the treatment response of patients with AD. Indeed, these genetic polymorphisms, either in the form of single nucleotide polymorphisms or direct changes to one or more amino acids, have been shown to cause differences in the therapeutic response. In summary, our findings indicate that genetic polymorphisms should be considered in the management of AD to achieve both effective and efficient treatment outcomes in terms of cost and prognosis.

Genetics of attention deficit hyperactivity disorder (ADHD)

Attention deficit hyperactivity disorder (ADHD) is not only highly prevalent, persistent and impairing but also is one of the most heritable of all psychiatric disorders. As a result, ADHD has been the focus of considerable genetic research. The results of recent genetic studies are reviewed with a focus on the emerging picture and future trends. ADHD appears to be a complex disorder in which multiple genetic and environmental risks

contribute to a quantitative trait. At the same time, there is growing evidence that in a proportion of cases, individually rare variants such as copy number variants may play an important causal role. The more genetic risks, both common and rare, the more extreme the trait. With increasing samples and advanced genetic methods, single nucleotide polymorphism (SNPs) and copy number variants (CNVs) conferring risk for ADHD are being identified. Further study will be required before we can understand the causal significance of these findings. Increased sample size is an urgent necessity if we are to discover potentially causal variants. Non-behavioral markers of genetic risk known as endophenotypes could also play a role in parsing the phenotypic and genetic heterogeneity of ADHD as they have in other complex disorders. Genetic studies in ADHD hold the potential for refined nosology, more precise diagnosis, and differential diagnosis, improved early identification leading to novel intervention strategies and identification of innovative targets for therapeutics based on a precise understanding of disease mechanism.

An update on COVID-19 pandemic: the epidemiology, pathogenesis, prevention and treatment strategies

To date, the transmission of Coronavirus Disease-2019 (COVID-19) is still uncontrollable with the fact that the numbers of confirmed and death cases are still increasing. Up to 1st October 2020, 33,842,281 confirmed cases and 1,010,634 confirmed deaths have been reported to the World Health Organization from 216 different countries, areas and territories. Despite the urgent demand for effective treatment strategies, there is still no specific

antiviral treatment for COVID-19 and the treatment guidelines for COVID-19 vary between countries.

Area covered

In this article, we summarized the current knowledge on COVID-19 and the pandemic worldwide. Moreover, the epidemiology, pathogenesis, prevention and different treatment options will be discussed so that we shall prepare ourselves better to fight with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

The situation of the COVID-19 pandemic is still unpredictable. There is no effective vaccine or specific anti-viral drug to treat serve COVID-19 patients. Combination therapies have shown promising clinical improvement. Repurposing FDA-approved drugs might be one of possible treatment options. Without specific treatment and vaccines for COVID-19, the most effective way to prevent from being infected is to generate an ecosystem with effective protection, precautions and preventive measures.

Update on the epidemiology, genetics, and therapeutic options of hyperuricemia

Hyperuricemia may occur when there is an excess of uric acid in the blood. Hyperuricemia may result from increased production or decreased excretion of uric acid. Elevated uric acid levels are a risk factor for gout, and various risk factors, including some medications, alcohol consumption, kidney disease, high blood pressure, hypothyroidism, and pesticide exposure, as well as obesity, are associated with an elevated risk of hyperuricemia. Although the mechanisms underlying the pathogenesis of hyperuricemia are

complex, previously reported studies have revealed that hyperuricemia is involved in a variety of biological processes and signalling pathways. In this review, we summarize common comorbidities related to hyperuricemia and describe an update of epidemiology, pathogenesis, and therapeutic options of hyperuricemia. This systematic review highlights the epidemiology and risk factors of hyperuricemia. Moreover, we discuss genetic studies on hyperuricemia to uncover current status and advances in the pathogenesis of hyperuricemia. Additionally, we conclude with a reflection on the underlying mechanisms of hyperuricemia and present the alternative drug strategies for the treatment of hyperuricemia to offer more effective clinical interventions.

Genetic causes and treatment of isolated growth hormone deficiency

Isolated growth hormone deficiency is the most common pituitary hormone deficiency and can result from congenital or acquired causes, although the majority of cases are idiopathic with no identifiable etiology. Known genes involved in the genetic etiology of isolated growth hormone deficiency include those that encode growth hormone (GH1), growth-hormone-releasing hormone receptor (GHRHR) and transcription factor SOX3. However, mutations are identified in a relatively small percentage of patients, which suggests that other, yet unidentified, genetic factors are involved. Among the known factors, heterozygous mutations in GH1 remain the most frequent cause of isolated growth hormone deficiency. The identification of mutations has clinical implications for the management of patients with this condition, as individuals with heterozygous GH1 mutations vary in phenotype and can, in some cases,

develop additional pituitary hormone deficiencies. Lifelong follow-up of these patients is, therefore, recommended. Further studies in the genetic etiology of isolated growth hormone deficiency will help to elucidate mechanisms implicated in the control of growth and may influence future treatment options. Advances in pharmacogenomics will also optimize the treatment of isolated growth hormone deficiency and other conditions associated with short stature, for which recombinant human growth hormone is a licensed therapy.

An update of current treatments for adult acute myeloid leukemia

Recent advances in acute myeloid leukemia (AML) biology and its genetic landscape should ultimately lead to more subset-specific AML therapies, ideally tailored to each patient's disease. Although a growing number of distinct AML subsets have been increasingly characterized, patient management has remained disappointingly uniform. If one excludes acute promyelocytic leukemia, current AML management still relies largely on intensive chemotherapy and allogeneic hematopoietic stem cell transplantation (HSCT), at least in younger patients who can tolerate such intensive treatments. Nevertheless, progress has been made, notably in terms of standard drug dose intensification and safer allogeneic HSCT procedures, allowing a larger proportion of patients to achieve durable remission. In addition, improved identification of patients at relatively low risk of relapse should limit their undue exposure to the risks of HSCT in first remission. The role of new effective agents, such as purine analogs or gemtuzumab ozogamicin, is still under investigation, whereas promising new targeted agents are under clinical development. In contrast, minimal advances have

been made for patients unable to tolerate intensive treatment, mostly representing older patients. The availability of hypomethylating agents likely represents an encouraging first step for this latter population, and it is hoped will allow for more efficient combinations with novel agents

Neuroblastoma in children update on clinicopathologic and genetic prognostic factors

Neuroblastoma is the most common extracranial solid tumor in childhood accounting for 8–10% of all childhood malignancies. The tumor is characterized by a spectrum of histopathologic features and a heterogeneous clinical phenotype. Modern multimodality therapy results in variable clinical response ranging from cure in localized tumors to limited response in aggressive metastatic disease. Accurate clinical staging and risk assessment based on clinical, surgical, biologic and pathologic criteria are of pivotal importance in assigning prognosis and planning effective treatment approaches. Numerous studies have analyzed the presence of several clinicopathologic and biologic factors in association with the patient's prognosis and outcome. Although patient's age, tumor stage, histopathologic classification, and MYCN amplification are the most commonly validated prognostic markers, several new gene mutations have been identified in sporadic and familial neuroblastoma cases that show association with an adverse outcome. Novel molecular studies have also added data on chromosomal segmental aberrations in MYCN nonamplified tumors. In this review, we provide an updated summary of the clinical, serologic and genetic prognostic indicators in neuroblastoma including classic factors that have consistently played a role in risk stratification of patients as well as

newly discovered biomarkers that may show a potential significance in patients' management.

Genetics of coronary artery disease

increases the risk of coronary artery disease in individuals with premature heart disease by twofold, and in the overall population the heterozygote is associated with a 25% increased risk and the homozygote with a 50% increased risk. It is of note that the risk mediated by 9p21 is independent of known risk factors. Since then, with the development of new technologies and the international consortium of CARDIoGRAM, there is now a total of 50 genetic risk variants confirmed and replicated for CAD. Of these 50, 35 mediate their risk by unknown mechanisms, indicating that the pathogenesis of atherosclerosis and myocardial infarction is due to additional factors as yet unknown. The role of genetic risk factors in the management of CAD is yet to be determined. Since many of them are independent of known risk factors, the genetic risk will in the future have to be incorporated into the guidelines, which recommend the target level of plasma LDL-C to be achieved based on the number of risk factors.

Update of genetic susceptibility in patients with Kawasaki disease

Kawasaki disease (KD) is an acute systemic vasculitis that predominantly affects children, and can result in coronary artery lesions (CAL). A patient with KD who is resistant to treatment with intravenous immunoglobulin (IVIG) has a higher risk of developing CAL. Incomplete KD has increased in prevalence in recent years, and is another risk factor for the development of CAL. Although the pathogenesis of KD remains unclear, there has been increasing evidence for the role of genetic susceptibility to the disease since it was discovered in 1967. We retrospectively reviewed previous genetic research for known susceptibility genes in the pathogenesis of KD, IVIG resistance, and the development of CAL. This review revealed numerous potential susceptibility genes including genetic polymorphisms of ITPKC, CASP3, the transforming growth factor-β signaling pathway, B lymphoid tyrosine kinase, FCGR2A, KCNN2, and other genes, an imbalance of Th17/Treg, and a range of suggested future treatment options. The results of genetic research may improve our understanding of the pathogenesis of KD, and aid in the discovery of new treatment modalities for high-risk patients with KD.

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