DR ALFRED GRECH, DR STEPHEN WEST, DR RAMON TONNA

Clinical Relevance of Pharmacoepigenetics

ABSTRACT

Epigenetics - defined as the inheritable changes that are not accompanied by alterations in DNA sequence - is a rapidly growing field and its research is being proposed for implementation into the clinical setting. Indeed, advances in epigenetics and epigenomics (which focuses on the analysis of epigenetic changes across the entire genome) can be applied in pharmacology.

Specifically, its application has given rise to a new specialty called pharmacoepigenetics, which studies the epigenetic basis for the variation between individuals in their drug response. Pharmacoepigenetics can become one of the tools for the personalised medicine approach, with potentially safer treatments and less side-effects on the horizon.

INTRODUCTION

Several research studies have shown that patients displaying similarities in disease expression may produce distinct responses to the same drug treatments. Although factors such as age, body-surface area, disease stage, gender or weight may be partly responsible, personalising treatments based on these factors does not completely tackle this problem. In fact, medical specialists are increasingly shifting in the direction of patient genomic data for selecting optimal treatments in specific scenarios. In addition, a growing body of evidence has revealed that epigenetics also plays a significant role in ascertaining the efficacy and safety of drug treatments in patients.[1]

Developments in epigenomics, including advances made by the Human Epigenome Project, have laid the foundations for the growing field of pharmacoepigenetics. Pharmacoepigenetics originally arose as a discipline to research how epigenetic patterns influence patients' drug responses. However, there is now another development for pharmacoepigenetics: therapeutic epidrugs designed to initiate changes in the epigenome, to reduce the symptoms or progression of a disease for individual patients. Notwithstanding the substantial knowledge gap that exists between our understanding of clinical treatments and epigenetic modifications on drug metabolism mechanisms, pharmacoepigenetics is a developing field with the potential to bridge the gap and be of great utility in personalised medicine.

PHARMACOEPIGENETICS AND HUMAN DISEASES

Underlying the development of effective epigenetic therapies are the epigenetic mechanisms and the proteins involved, including DNA methylation, histone modifications and regulatory miRNA.[2] DNA methylation is closely linked with histone modifications, and their interaction is fundamental in controlling genome functioning by altering chromatin architecture. In addition, a group of miRNAs known as epi-miRNAs can directly target effectors of the epigenetic machinery, including DNA methyltransferases, histone deacetylases (HDACs), and polycomb repressive complex genes. Such epigenetic-miRNA interaction results in a new layer of complexity in gene regulation, opening up new avenues.

In this article, we will discuss briefly how these mechanisms link to diseases such as cancer, heart and neurodegenerative diseases, autism, bipolar disorder, depression and immunological disorders.

Cancer

It is true that, when it comes to the epigenetic aberrations of particular cancers at different steps in tumour development, a lot of work still needs to be carried out. It is also true, however, that there is a general understanding of which modifications lead to irregular gene expression in relation to the different types of cancer. In fact, these epigenetic biomarkers are being applied in the clinic as a tool to first detect cancer and classify the tumour, and then to understand the drug response to treatment.

As an example, the DNA methyltransferase inhibitors azacitidine and decitabine have been approved by FDA for the treatment of patients with acute myeloid leukaemia, chronic myelomonocytic leukaemia and higher-risk myelodysplastic syndromes; the latter being a group of cancers where blood cells from the bone marrow do not mature properly into healthy blood cells.[3,4]

Azacitidine, together with another drug called entinostat, has also been used in clinical trials of non-small-cell lung carcinoma.[5] In this particular study, 4 out of 19 patients had major objective responses to anticancer therapies given directly after epigenetic therapy. Entinostat, a HDAC inhibitor, prevents gene silencing by allowing access to the transcription machinery. Entinostat has also been shown to be a promising treatment for patients with advanced breast cancer.[6]

MiRNA-based therapeutic strategies have also been applied in cancer. For example, a new miRNA drug candidate called RGLS5579 that targets miR-10b has been announced for potential trials in patients diagnosed with glioblastoma multiforme, one of the most aggressive forms of brain cancer.[7]

Heart Disease

In the developed world, mortality and morbidity from cardiovascular diseases (CVDs) represent a large burden to society.[8,9] CVDs such as *atherosclerotic cardiovascular disease*, cardiomyopathy, congenital heart disease, heart failure and hypertensive heart disease are now being tackled as much more multifaceted disorders. Indeed, the epigenetic research in this field is now more prevalent and histone modifications and miRNAs have also been found to have a key role in heart disease.[10]

In 2016, Somanna et al. published the findings of their study which used the HDAC inhibitors Trichostatin A and Mocetinostat to show that targeting HDACs weakens the pro-fibrotic and pro-inflammatory effects of angiotensin (Ang)-II on adult mouse cardiac fibroblasts.[11] In addition, there is an increasing number of publications showing that miRNAs play a significant role in numerous aspects of heart failure. One such study is that by Yang et al. (2019), who found that miRNA-19b-1 reverses ischaemia-induced heart failure by inhibiting the apoptosis of cardiomyocytes.[12] In a different study, Verjans et al. (2019) identified miRNAs as multi-cellular regulators of different processes that cause cardiac disease. Specifically, they characterised formerly undescribed roles of miRNAs in fibrosis, hypertrophy and inflammation, and ascribed novel effects to many well-known miRNAs.[13]

Neurodegenerative Disorders

Brain disorders with a vascular and/or neurodegenerative constituent are a common problem worldwide. One way in which this could be mitigated is through pharmacoepigenetics.

DNA methylation could be restored, for instance, to regenerate the metabolic pathways disturbed by DNA hypomethylation, which is linked with the progression of some of the most widespread neurodegenerative disorders, including Alzheimer's and Parkinson's disease. Indeed, the ability of S-adenosyl-L-methionine and the B vitamins, including folic acid, to restore methylation, together with their brain protective properties, makes them good diet supplements for treating these diseases. Currently, vitamin B6 and folate are proposed for clinical trials to ascertain whether these interventions could possibly decrease cognitive impairment in patients with Alzheimer's disease.[14]

HDAC inhibitors could also restore histone deacetylation, which is a shared feature of numerous neurodegenerative processes. In animal models, several HDAC inhibitors under development offer beneficial effects for cognitive and memory levels of Alzheimer's and Parkinson's diseases. However, only nicotinamide, sodium phenylbutyrate and valproic acid are in clinical trials as epidrugs for treating neurodegeneration.[14,15]

MiRNAs also play a role here. For instance, the overexpression of miR-124[16] and miR-195[17] decreases the levels of the -amyloid (A) plaques, which are known to cause the neurodegeneration in Alzheimer's disease. In addition, miR-323-3p[18] has been found to decrease neuroinflammation related to Alzheimer's disease. Other non-coding RNAs, such as miR-34b/c, miR-132, and miR-221, are also possible biomarkers and therapeutic targets for Parkinson's disease[14,19].

Autism Spectrum Disorder

Autism spectrum disorder (ASD) is used to describe development disorders caused by a combination of genetic and environmental factors. Recently, the multigenic condition of ASD has been speculated to depend on epigenetic effects[20], although this remains unclear.

For this reason, pharmacoepigenetics in ASD is still in its early stages. While research on epigenetic predictors of drug response is rare in ASD, the data on the development of epidrugs is encouraging. DNA methyltransferase inhibitors have been found to reactivate repressed genes in autism-associated genetic conditions, and more precisely, RNA-therapeutic targeting genes were used to reactivate MeCP2, which is a candidate gene of ASD. In animal studies, HDAC inhibitors have also been shown to enhance cognitive impairment and social behaviour.[21]

Bipolar Disorder

Studies have also been investigating the role of epigenetic mechanisms in bipolar disorder and its treatment. Some of these mechanisms have been shown to be involved in the action of antidepressants, antipsychotics and mood stabilisers used for treating patients with bipolar disorder.[22]

In a paper published in 2015, Backlund et al. investigated whether DNA methylation levels vary between healthy controls and bipolar patients when treated with either lithium or a combination of lithium and valproate, both of which are mood stabilisers. The authors found that lithium in monotherapy was linked to hypomethylation, whereas lithium and valproate displayed a hypermethylated pattern when compared to lithium alone.[23] This suggests that the choice of treatment in bipolar disorder may lead to different levels of DNA methylation. However, more research is necessary to understand its clinical significance. Having said that, these epigenetic biosignatures could eventually revolutionise this field and benefit patients and clinicians alike in the future.

Depression

Major depressive disorder has become a worldwide problem, with more than 50% of those on an initial antidepressant course not showing symptom remission. A genetic basis for the pathophysiology of major depressive

disorder has been strongly indicated in research studies, but despite these breakthroughs, no biomarkers have been satisfactorily validated in treatment responses from clinical practice.[24]

New evidence from both human and animal model studies indicates a prominent role of epigenetic marks, such as histone modifications and DNA methylation, in predicting response to antidepressants. For example, epigenetic modifications of the genes SLC6A4, IL11 and BDNF are demonstrating encouraging signs as biomarkers to predict antidepressant response.[25]

Immunological Disorders

It has been shown that altered epigenetic patterns also play an important role in the development and pathophysiology of immunological disorders, especially autoimmune diseases.[26]

Indeed, HDAC inhibitors have been used in autoimmune disorders, such as rheumatoid arthritis (RA), systemic lupus erythematosus and systemic onset juvenile idiopathic arthritis.[27,28] For example, a study revealed a new molecular mechanism by which the HDAC inhibitor Trichostatin A can disturb inflammatory cytokine production in RA synovial cells, suggesting that targeting HDACs may be useful in suppressing inflammation in RA in a clinical setting.[29]

It has also been suggested that DNA methylation contributes to the development of RA, however, with contradictory and unsatisfactory results. Studies have also shown that circulating cell-free methylated DNA in blood offers a non-invasive "liquid biopsy", providing a template for assessing molecular markers of diseases, including RA. Epigenetic therapies controlling autoimmunity may therefore find far-reaching implications for the diagnosis and management of RA.[30]

CONCLUSION

We know that responses to therapeutic treatments are greatly dependent on our individual genomic and epigenomic profiles, and so personalised treatments ideally should be governed by pharmacogenetic and pharmacoepigenetic methods for optimal efficacy. However, because the epigenetic machinery is versatile, manipulations of epigenetic aberrations may lead to drug resistance.

In the emergent field of pharmacoepigenetics, there is a current lack of information regarding the long-term consequences of epidrugs exploiting targets with no real cell specificity. In fact, procedures must first integrate pharmacoepigenetic studies in order to evaluate safety concerns and treatment efficacy in developing drugs and subsequent clinical trials.

Despite recent major strides in the field of pharmacoepigenetics, it is only after further investigation that we will fully understand the role of epigenetic modifications in human health, such that we can harness its potential power for personalised treatment of disease.

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