World Journal of Stomatology

Online Submissions: http://www.wjgnet.com/esps/
bpgoffice@wjgnet.com
doi:10.5321/wjs.v2.i4.67

World J Stomatol 2013 November 20; 2(4): 67-70
ISSN 2218-6263 (online)

EDITORIAL

Pharmacogenomics in oral diseases

Sridharan Gokul, Gokul Sapna

Sridharan Gokul, Oral Pathology and Microbiology, YMT Dental College and Hospital, Kharghar, Navi Mumbai-410210, Maharashtra, India
Gokul Sapna, Department of Periodontics, Nair Hospital Dental College, Mumbai-400008, Maharashtra, India
Author contributions: Gokul S formulated the idea of writing the editorial; Gokul S and Sapna G together performed literature review and collected relevant data; Sapna G also contributed in proof reading the manuscript.
Correspondence to: Sridharan Gokul, MDS, Lecturer, Oral Pathology and Microbiology, YMT Dental College and Hospital, Kharghar, Institutional area, sector-4, Kharghar, Navi Mumbai-410210, Maharashtra, India. drgokuls@gmail.com
Telephone: +91-22-27744429 Fax: +91-22-27744427
Received: April 6, 2013 Revised: July 11, 2013
Accepted: July 17, 2013
Published online: November 20, 2013

Abstract

The availability of newer technologies for identification and characterization of the human genome has enabled our understanding of the genetic variations in a majority of human diseases. Human genomic sequence varies in less than 1% among the different population group and these differences known as gene polymorphisms are the primary reasons for differences in individuals' response to various drug therapy. Also understanding the genetic changes may enable implementation of targeted therapy, thus providing for effective treatment strategies and minimizing the adverse side effects. Pharmacogenomics is a recent development in the field of personalized medicine which focuses on the genetic determinants of drug response at the levels of entire human genome. It primarily deals with tailoring of drug therapy for every individual based on their genetic make-up and identifying new target in various diseases for drug therapy. While the application of pharmacogenomics in systemic illness is well researched, its role in oral diseases needs documentation. Identifying specific targets in periodontitis, head and neck cancer, infections and genetic disorders can be beneficial in discovery of new drugs. This editorial provides an overview of basics of pharmacogenomics, its current role in disease management and its potential role in various head and neck diseases.

Key words: Pharmacogenomics; Oral Cancer; Periodontal diseases; Genomic variations; Targeted drug therapy

Core tip: Pharmacogenomics mainly focuses on the genetic determinants of drug response at the level of entire human genome. It primarily deals with tailoring of drug therapy among every individual based on their genetic make-up and identifying new targets in various diseases for drug therapy. Identification of gene polymorphisms in humans will aid in modulating drug therapy for individual needs as well as leading to discovery of target drugs. This editorial provides an overview of basic pharmacogenomics and its usefulness in oral diseases.

Gokul S, Sapna G. Pharmacogenomics in oral diseases. *World J Stomatol* 2013; 2(4): 67-70 Available from: URL: http://www.wjgnet.com/2218-6263/full/v2/i4/67.htm DOI: http://dx.doi.org/10.5321/wjs.v2.i4.67

INTRODUCTION

Pharmacogenomics is a component of individualized medicine focusing on how genetic factors influence individual responses to different medications that may affect drug efficacy, side effects and adverse events to drug therapy[1]. The aim of pharmacogenomics is to decrease adverse responses to therapy through determining new therapeutic targets and genetic polymorphisms that affect drug specificity and toxicity[2]. The term pharmacogenomics, a relatively new term is often used interchangeably with a much older term pharmacogenetics though differences exist between the two terms. While pharmacogenetics refers to the study of how individual genes in-

fluences the response to medications, pharmacogenomics is related to the study of how individuals' genomic composition as a whole affects their response to medicine[3]. The field of pharmacogenomics uses genetic and genomic information of individuals in order to predict the response of patient groups to drugs and thus guide clinical trial and the drug development process. This can be made possible with the development of human genome project which encodes majority of human genes.

Most of the commonly occurring diseases such as cancer, atherosclerosis and neurodegenerative disorders comprise of a group of genetically discrete entities with separate molecular etiologies and possibly different responses to therapy. Pharmacogenomic therapy has been attempted to treat cystic fibrosis[4], acquired immune deficiency syndrome (AIDS), cardiovascular diseases, psychiatric illness and targeted therapy towards epidermal growth factor receptor (EGFR) for treatment of pancreatic cancer[5] and non small cell lung carcinoma[6]. In addition to the development of new therapeutic agents, pharmacogenomics can also predict outcomes and beneficial therapy regimens. The various targets that are extensively studied are angiotensin converting enzyme regulating cardiovascular functions; analyzing the association between β2 adrenergic receptor polymorphism and asthma[7] and use of apolipoprotein polymorphisms to predict the risk of heart disease and response to treatment[2].

Most of the disorders affecting the head and neck region excluding trauma have genetic implications in various forms. The disorders range from developmental disturbances, microbial infections and bone disorders to various forms of head and neck cancers. An understanding of the genetic changes occurring in these disorders may be helpful in implementation of drug therapy aiming to obtain maximum efficacy with minimum side effects and also to evolve targeted drug therapy for the management of such lesions.

BASICS OF PHARMACOGENOMICS

A gene is defined as a specific sequence of nucleotide bases whose sequences carry the instructions for the constructions of proteins. Hundreds of genes reside on each chromosome and the complete human genome is estimated to contain about 30000 genes[8]. More than 99% of DNA sequence is the same across the entire human population. The small genetic dissimilarities have a major impact on persons' physical makeup and response to disease as well the effectiveness of the therapy instituted. Pharmacogenomic technologies try to detect these genetic variations in a patient or patient populations to help select drug compounds and doses that are more likely to work.

These genetic variations which account for around 1 million of the 3 billion bases of human genome are termed as polymorphisms. Polymorphisms arise from three fundamental types of DNA sequence variations namely single nucleotide polymorphisms (SNPs) representing nucleotide substitutions, insertions or deletions and indel of repetitive DNA[9]. Advances in pharmacogenomics mainly depend on identification of SNPs in the human genome. These arise from mutations affecting a single nucleotide, occurring relatively frequently and must exceed in a population of a frequency of 1% to meet the requirement of genetic polymorphism[10]. The main research use of a human SNP map would be to determine the contributions of genes to diseases that have a complex multifactorial basis. More than 1.4 million SNPs have been identified in human genome till date[8]. Majority of the genetic polymorphisms are found in drug metabolizing enzymes, receptors and transport proteins and produce varying effects on drug metabolism[2]. The use of these genetic variations in order to individualize drug therapy and to identify novel targets to enable the development of new drugs for various diseases are the primary reasons for which pharmacogenomics is employed.

Drugs in the body are metabolized by enzymes and most of the enzymes belong to the members of cytochrome P450 (CYP) system. These enzymes are located in the liver and gastrointestinal tract and include greater than 30 isoforms[11]. Individual variations in the genes that produce these enzymes causes different people to metabolize the same drug differently; less active or inactive forms of CYP enzymes that are unable to breakdown and efficiently eliminate a drug from the body (slow metabolizers) can cause the drug to build up while very active forms (rapid metabolizers) can cause the body to clear itself of a drug before it has a chance to work[12]. Understanding an individuals' response to a certain drug can help the clinician to decide the accurate drug dosage required for effective therapy thereby reducing the chances of overdose or insufficient dosage. Of all the types of CYPs, most of the functional genetic polymorphisms reside in only few of them namely CYP3A4, CYP2A6, CYP2C9, CYP2C19 and CYP2D6[10]. Of these, CYP3A is involved in the oxidative biotransformation of up to 50% of clinically important therapeutic agents that has resulted in the withdrawal of important drugs like Mibefradil (anti-hypertensive drug), Rezulin (oral anti-hyperglycemic agent) and propulsid (for treatment of gastrointestinal disorders).

Other less common polymorphisms can be seen in drug transport proteins and receptors. Transport proteins are proteins that allow compounds to be transported across cell membranes and P-glycoprotein is a drug transport protein known to be involved in the metabolism of many drugs[13]. Identifying this polymorphism would be a valuable tool in determining therapeutic concentrations required for individual patients. Receptors polymorphisms are helpful for development of new therapeutic agent and to predict outcomes and beneficial treatment regimens. Some of the common receptor targets that have been targeted by the use of drugs include angiotensin converting enzyme, β2-adrenergic receptor polymorphism, cystic fibrosis transmembrane conductance regulator and p53 and EGFR for anti-cancer therapy.

APPLICATIONS OF PHARMACOGENOMICS IN ORAL DISEASES

Genetic mutations are a common finding in majority of the human diseases affecting the head and neck region. which may contain one or many genetic polymorphisms. Examples of disorders exhibiting single gene mutations include Treacher-Collins syndrome, Pierr-Robin syndrome, Crouzon syndrome, Ectodermal dysplasia, achondroplasia and Gorlin syndrome while cleft lip and palate, congenitally missing teeth, dental caries, severe malocclusion, head and neck cancer, periodontal diseases and autoimmune disorders are caused by multiple gene mutations[14].

Chemotherapeutic intervention for cancer therapy is undergoing changes from being an empiric random screening approach to a target directed approach where specific abnormalities in cell functioning are modulated in a drug receptor fashion. The use of small molecules with tyrosine kinase inhibitory activity directed towards the EGFR such as gefitinib and erlotinib are used for treatment of NSCLC, pancreatic and breast cancer[5]. EGFR is a transmembrane glycoprotein member of erbB family of type I tyrosine kinase which plays a crucial role through downstream signaling pathways in cell cycle progression, survival and proliferation[15]. Overexpression of EGFR in head and neck cancer are known to be associated with poor prognosis and hence the use of drugs such as tyrosine kinase inhibitors may help in improving the prognosis and survival rate. Adequate understanding of the molecular mechanisms involving various growth factors (such as transforming growth factor, platelet derived growth factor, hepatocyte growth factor), cytokines and genetic mutations occurring in carcinogenesis will aid in the development of chemotherapeutic drugs against specific targets for appropriate management and to reduce patient morbidity and mortality.

Periodontitis is a polymicrobial infection resulting from a complex interaction between oral microbes and host immune response leading to periodontal destruction and alveolar bone resorption. The host response to infection is primarily in the form of inflammatory reaction leading to release of various cytokines, growth factors and matrix metalloproteinases (MMP). Identification of therapeutic targets which are directed towards the specific host alteration may be helpful as an adjuvant treatment for periodontitis. Monoclonal antibody derivatives directed towards MMP are promising as therapeutic agents and mainly involves non-antimicrobial activities of low dose tetracycline and tetracycline analogue doxycycline hyclate via the inhibition of MMP-8 and -13 protease mechanisms. The therapeutic action of these agents is primarily due to the modulation of the host response because the low dose formulations of these drugs have lost their antimicrobial property[16]. Research in targeted therapy are also underway for treatment of various other microbial infections like candidiasis, birth defects, orthodontic tooth movements but are still at initial stages.

To summarize, decoding the human genome with aim to describe genetic changes in various oral diseases will be beneficial in providing appropriate therapy. The use of pharmacogenomics in determining the functioning of various drugs in individual patients will be a boon for clinicians to decide the appropriate dosage. Research concerning targeted drug therapy has advanced exponentially and could be ideal for treatment of diseases like cancer and AIDS without major side effects and also for management. This has been enhanced by the availability of advanced technologies such as SNPs and DNA microarrays which helps in analyzing genetic changes.

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P- Reviewers: Arabaci T, Vaidya MM **S- Editor**: Wen LL
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