Macedonian pharmaceutical bulletin, 68 (Suppl 1) 353 - 354 (2022)
Online ISSN 1857 - 8969
DOI:10.33320/maced.pharm.bull.2022.68.03.170
Short communication

Novel insights in pharmacomicrobiomics

Filip Djokoski*, Marija Hiljadnikova-Bajro

Faculty of Pharmacy, Institute of Applied Biochemistry, Ss. Cyril and Methodius University in Skopje, Mother Theresa 47, 1000 Skopje, Republic of North Macedonia

Introduction

The human microbiome is specific to each person and has a significant influence on the individual growth and development as well as the development of the immune system and susceptibility to diseases.Unlike the human genome, the human microbiome is quite inconsistent, being constantly subject to changes throughout the life of an individual due to many influential factors such as: age, environment, genetics, diet, xenobiotics (especially antibiotics), mode of birth, breastfeeding duration, physical and mental stress, and the influence of individual lifestyles (‘‘The Microbiome and Public Health’’, n.d.). Deciphering the mechanisms of the microbiome affects the health (development and progression of certain diseases) of individuals and how it affects a given medication, allows us to improve the implementation of personalized medicine for early detection or prognosis of the clinical outcome in a specific disease, as well as the development of an appropriate therapeutic strategy. Recent data from the published literature in this field, indicate that the metabolizing of drugs (xenobiotics) by the gut microbiota, strongly affects the effectiveness and toxicity of certain types of therapeutics.

Clinical implication

Drug metabolism takes place in several separate phases: Phase 1 (functionalization – involving enzymes in liver, gut and other tissues, mainly mediated by CYP450), phase 2 (conjugation) and phase 3 (ABC transporter) (Abdelsalam et al., 2020). However, today we alsoknow that an abundance of enzymesis being synthesized by the gut microbiota and they can activate (sulfasalazine), inactivate (some antibiotics), reactivatea drug or convert it into a toxic metabolite.The gut microbes usually conduct hydrolytic and reductive reactions to produce metabolites with a lower polarity and molecular weight thus affectingthe bioavailability of over 30 drugs through transformation oftheir chemical structures. The gut microbiome is confirmed to be involved in the metabolism of some antihypertensive drugs including: oxidation of amlodipine and nifedipine, deacetylation of diltiazem, deglucuronidation of losartan and de-esterification of enalapril (Chenet al., 2022). In the study of Liet al. (2016) one cansee that the gut microbiota affects about 40 drugs and natural products that have been reported. In this study it is also well clarified the metabolizing of digoxin by *Eggerthellalenta*(an anaerobic bacterium of the normal human flora), influences of microbiota variation on acetaminophen metabolism / acetaminophen-induced hepatotoxicity and therapeutic difference of statins, the reduced side effect of irinotecan by microbiota depletion and the modulation of the effectiveness of chemotherapeutics by the gut microbiota. As the drugsreach the intestines after oral administration, they can be metabolized by the intestinal microbiome through the processes of oxidation, reduction, hydrolysis, dihydroxylation, O-dealkylation, deacetylation, demethylation, decarboxylation, acetylation, deamination, deconjugation and before their absorption they can be metabolized further in the intestinal mucosal and subsequently in the liver (Wilson and Nicholson, 2017). The drug L-dopa is metabolized by *Enterococcus faecalis* (PLP-dependent decarboxylase / tyrosine decarboxylase) to dopamine and then is metabolized by *Eggerthellalenta* (Mo-dependent dehydroxylase / dopamine dehydroxylase) to m-tyramine (Jameson andHsiao, 2019). Some bacterial cells express adhesive proteins called adhesins, responsible for binding to the host cells but also capable to bind and interact with the drug molecules (e.g., levodopa and *H. pylori*). Dhurjad et al. (2022) recentlydemonstrated that the intestinal microbiota can cause: alteration in the absorption of drugs (by microbiota

*Filip_Djokoski@hotmail.com

metabolites that change the local microenvironment in the human gut), competition of microbial metabolites with the drug or host metabolites for binding with the active sites of the host's metabolic enzymes, modification of the expression of host's genes crucially involved in drug metabolism and immunomodulation (impact on efficacy of chemotherapeutic drugs by translocation and immunomodulation). The most distinguished microbiome-drug associations for the time being involve: l statins, β-blockers, angiotensin-converting enzyme (ACE) inhibitors, proton-pump inhibitors, laxatives, metformin and selective serotonin reuptake inhibitors (Weersma et al.,2020). The microbiome-derived acarbose kinases provide their harboring organism with a protective advantage against the activity of acarbose and thus attribute resistance of the microbiome to a non-antibiotic drug (Balaich et al., 2021). Antipsychotics (APs) in addition to their proven antibiotic effect, can affect the gut microorganisms by altering the pH of the gastrointestinal tract and changing its mucosal integrity and permeability. Numerous neurotransmitters (gamma-aminobutyric acid, serotonin, noradrenaline and dopamine) are produced by gut microbes and are able to travel to the brain where they directly impact the action of drugs on brain neurotransmitter receptors (Seeman, 2021). Schupack et al. (2022) have recently shown the potential implication of the human microbiome in clinical practice as a tool to develop individualized strategies for the treatment of certain diseases, opening a new opportunity for the advancement ofpersonalized medicine. Several studies have also shown the effect of gut microbiota on the outcome i.e., efficacy and toxicity of chemotherapeutic and immunotherapeutic agents like immune checkpoint inhibitors. Many approaches like the use of antibiotics, probiotics, prebiotics, synbiotics, postbiotics, dietary modulation and fecal microbiota transplantation, have shown potential in optimizing cancer treatment outcomes and these findings can provide predictive biomarkers of cancer treatment responses, to be employed in the selection of appropriate anticancer therapy in future (Ting et al.,2022). It is known that lipopeptides produced by some microorganisms show anticancer effects and they can serveas a model in the process of drug development to design drugs that the body would easily accept (a drug produced by human microbes that live in a synbiotic relationship with the human body) (Chauhan and Kanwar, 2021).

Conclusion

The field of pharmacomicrobiomics as one of the innovative "omics" approaches in diagnosis, treatment monitoring and drug development, represents a historic step forward towards the establishment of personalized medicine since its clinical application will not only improve public health but can also provide appropriate prognostic and predictive tools in the scope of individualized therapy as well as point to interventions that should be done on the microbiome in order to improve the outcome of a given therapy.

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