NEW BLOOD

Moving from Association to Causation: Deciphering the Role of the Gut Microbiota in Hypertension

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The gut harbours trillions of microbes including bacteria, fungi, and viruses, collectively known as the gut microbiota. These microbes interact among themselves, but also with the host's immune system and environment (e.g. food). There is increasing evidence to support the role of the gut microbiota and its genome, the gut microbiome, in hypertension[1]. Despite the increasing number of microbe-wide association studies (MWAS), identifying specific causal microbes that contribute to blood pressure (BP) regulation has been challenging[2,3]. This is unsurprising given our experience with genome-wide association studies (GWAS), which have identified hundreds of genes with little understanding about their role in BP control per se[4]. Considering the gut microbiota is influenced by many intrinsic (e.g., host's genetics[5]) and extrinsic factors (e.g. diet, geography, ethnicity, seasonal variations, circadian cycle, and medication use), gut microbiome studies require careful experimental design. This is easier done using laboratory animals than humans[6].

Instead of identifying causal microbes, a more fruitful approach is to assign functions to microbes to better understand their roles. Through this approach, it was shown some bacteria, such as butyrate-producers, are lacking in hypertensive patients. Indeed, we recently discovered that microbial gene pathways might be more important than specific microbial taxa[7]. This has also led to the discovery of the importance of metabolites such as short-chain fatty acids (SCFAs) in hypertension[8] and trimethyl-amine oxide (TMAO) in cardiovascular diseases[9].

To further advance the field, mechanistically linking microbes or metabolites to function and phenotype is essential. There are multiple ways to achieve this, namely a) reverse microbiome approaches, b) forward microbiome approaches, and c) microbe-phenotype triangulation (Figure 1)[9].

An example of the use of these approaches is a recent publication in Circulation Research, by Dr. David Durgan and his team. They elegantly employed some of these approaches to demonstrate mechanistically how the gut microbiota changes with intermittent fasting and how that influences BP[10]. Using a forward microbiome approach, they first compared the gut microbiome between their experimental groups and identified differentially abundant bacteria that metabolised bile acid. To confirm this, they performed caecal and plasma metabolomics and found evidence supporting differences in bile acid metabolites. Armed with sufficient evidence, they went on to use a reverse microbiome approach to confirm their findings by dietary supplementation and agonist treatment. By using a combination of these methods, they were able to pinpoint that increased BP in hypertensive rats was a result of reduced plasma bile acid levels which could be restored with either a) intermittent fasting, b) supplementing cholic acid (precursor of bile acids) or c) agonist treatment of TGR5, a bile acid receptor. Although their studies were not validated in the context of human hypertension, a recent clinical study showed fasting influenced the gut microbiome and reduced BP in patients with metabolic syndrome[11]. However, altered bile acid metabolism was not discovered in those patients, potentially because of differences in the models and diet.

Moving forward, a push towards identifying causal links of the gut microbiome in hypertension is necessary to advance the field. Confirmatory experiments need to be performed and validated in other models and ideally in clinical interventional studies.

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