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Metabolic Syndrome, Gut Microbiome and Dietary Bioactive Peptides, an Unexplored Triad



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Rohita Sinha,^{1*} Jennifer Clarke,^{1,2} Jean-Jack Riethoven^{3,4}

ABSTRACT

The gut microbiome is a complex, biochemically rich and essential component of the human metabolic system. It has been our understanding for very long that the gut microbes are primarily there to digest the undigested food (mainly fibers), get nourishment, and in return release metabolites helping host cells — short-chain fatty acids produced by gut microbes are a great source of energy for the colonocytes. It is only in the last decade, with advancements of DNA

sequencing platforms, that we are lettered about the association between the gut microbial composition and metabolic disorders such as obesity, dysglycemia, dyslipidemia, and cardiovascular diseases. This creates a momentum to understand the factors shaping the composition of the gut-microbiome, nature of dysbiosis (perturbation of gut microbial composition) associated with human health and ways to modulate the gut microbiome to achieve the desired health benefits

Keyword: gut microbiome, obesity, bioactive peptides

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GUT MICROBIOME AND METABOLIC SYNDROME

The gut microbiome is a complex, biochemically rich and essential component of the human metabolic system.¹ It has been our understanding for very long that the gut microbes are primarily there to digest the undigested food (mainly fibers), get nourishment, and in return release metabolites helping host cells — short-chain fatty acids produced by gut microbes are a great source of energy for the colonocytes.^{2,3,4} It is only in the last decade, with advancements of DNA sequencing platforms, that we are lettered about the association between the gut microbial composition and metabolic disorders such as obesity, dysglycemia, dyslipidemia, and cardiovascular diseases.^{5,6,7} This creates a momentum to understand the factors shaping the composition of the gut-microbiome, nature of dysbiosis (perturbation of gut microbial composition) associated with human health and ways to modulate the gut microbiome to achieve the desired health benefits.^{8,9,10}

DIET, A PREDOMINANT FACTOR SHAPING THE GUT MICROBIOME

Since microbes colonize gut mainly for nutrients, diet was hypothesized to be one of the predominant factors shaping the gut microbial composition. In

last few years, this hypothesis was tested by multiple individual groups and reported a direct association between specific diet-types and gut microbial composition.^{1,11,12,13,14} Jansson/Tanja et al¹⁵ have found that a diet rich in resistant starch (RS) modulates the Firmicutes and Bacteroidetes ratio. A comparison of animal and plant based diet has shown that even a short term perturbation of diet may change the composition of the gut microbiome, and animal-based diet boosts the abundance of bile-tolerant microbes and decreases Firmicutes which uses polysaccharides from plant sources.¹⁶ Similar observation of quick changes in microbial composition has been found through the Western-diet (high Fat and Sugar).¹⁷ Therefore, a dietary modulation of gut-microbiome to treat above discussed metabolic disorders is an experimental hypothesis tested at the limited scale by several independent labs. A majority of these dietary interventions were about feeding prebiotics, which is described as the food supplements for the gut microbiome. Typically fibers, indigestible to host, are used as prebiotics and have been found to have positive impact on specific members of gut-microbiome.^{18,19,20}

BIOACTIVE DIETARY MOLECULES

Food is obviously our prime source of essential nutrients and plays a predominant role in

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determining our health status. While existing literature has a comprehensive report about the health benefits of various food articles, our knowledge about the molecular-mechanisms exerting these benefits is still at its infancy. Advanced techniques such as Next generation sequencing, has certainly helped us untangle the complex association between diet and the gut microbiome, which consequently affects the physiological state of the human being. One of the these less explored class of bioactive molecules and molecular-mechanisms are dietary peptides and their mode of action.

Bioactive peptides:

Bioactive peptides are part of scientific exploration since the last three decades; and almost all levels of living entities such as microbes, plants, and animals either produce or have proteins that are digested to bioactive peptides by proteases.²¹ For example, serum albumin treated with trypsin produces peptides with antihypertensive and antioxidant activities, similarly plant sources such as wheat, rice, oat, sorghum etc. were reported to be rich sources of bioactive peptides.^{22,23} There are several reports of milk and other dairy products as a reservoir of bioactive peptides.^{24,25} The range of activities of known bioactive peptides are comprised of antihypertensive, antioxidant, anti-inflammatory and antimicrobial actions.^{26,27} Among these, the antimicrobial activity of bioactive peptides draws a lot of attention, as the frequency of microbial resistance to known drugs is increasing. Antimicrobial peptides (AMP) originated from the animal system are considered as the first line of defence in the area with constant exposure to pathogenic microbes. AMPs are natural product of several prokaryotes and eukaryotes and so far more than 5000 such peptides are reported in the literature.^{28,29,30} The most common mode of action of AMPs is dependent on their ability to interact with the negatively charged cell surface of the microbes and then insert into the hydrophobic cell membrane and disrupt it either by creating pores or making clusters. There is another class of AMPs which are absorbed (cell penetration or endocytosis) by the microbial cells and exert their activities by disrupting essential biochemical pathways.^{31,32,33,34}

Antimicrobial peptides with intracellular activities

Beyond the common perception of antimicrobial peptides acting as microbial cell-surface disrupter, there is ample evidence of peptides with intracellular activities.^{32,33,34} Following are examples of antimicrobial peptides with intracellular activities:

Buforin I/II: Buforin-I is a 39 amino-acid long AMP derived from the stomach of the *Bufo bufo*

gargarizans, an Asian toad.³⁵ While Buforin-I has a broad spectrum antimicrobial activity, its 21 amino-acid long derivative (Buforin-II) was found to be more potent. Contrary to the majority of known AMPs, Buforin-I/II interacts with DNA & RNA to kill the microbes.³⁶

Apidaecin type peptides: These peptides are generally 18-20 amino acids long and were isolated from honeybees.^{37,38} Predominantly uptaken through the ABC transporters of Gram-negative bacteria, Apidaecin peptides bind to ribosomes to disrupt bacterial protein synthesis.³⁹

Bac7: A 60 amino-acids long peptide derived from the bovine neutrophils. Bac7 does not disrupt bacterial cell membrane, but rather travels to the cytoplasm with the help of peptide transporter protein Sbm-A. Bac7 kills bacterial cells by targeting ribosomes and hindering protein synthesis.⁴⁰

Indolicidin: It is a 13 amino-acids long peptide derived from the bovine neutrophils. It interacts with double stranded DNA molecules to arrest transcription, replication and consequently kills the bacterial cell.^{41,42}

PEPTIDES AS NATURAL INHIBITORS OF PROTEIN-PROTEIN INTERACTIONS (PPIS)

As discussed above, there are several yet to be defined biochemical interactions or 'mode of actions' of bioactive peptides — competitive inhibition of vital protein-protein interactions is one of them. Protein-protein interactions (PPI) are essential to most of the vital cellular-pathways such as transcription, translation, signal transduction, host-pathogen interactions, etc.,⁴³ and are emerging as a new class of drug targets. Thus, recently we have seen a wider effort to develop an array of PPI inhibitors (antibodies, small-ligands and peptides)^{44,45,46} and extend the concept to develop microbial PPI inhibitors as a new class of antimicrobial agents.

Cellular protein-protein interaction networks are marked by the presence of hub proteins — proteins which interact with multiple individual proteins. Such proteins are vital to entire networks, and consequently are prime targets for the antimicrobial agents. Protein-protein complexes are characterized by larger interfaces, where the interactions are mediated by several short fragments (peptides). Few of these interfacial peptides called hot-segments, contribute most to the total binding energy of these complexes. The hot-segments are used as lead-molecules to develop new PPI inhibitors.^{47,48,49} Few of the several such successful cases are inhibitory peptides for P53 & MDM2⁵⁰ and XIAP & Smac interactions;⁵¹ there

are also instances of peptides inhibiting oligomerization of membrane proteins.^{52,53}

TRIAD OF METABOLIC DISORDERS, GUT MICROBIOME AND DIETARY PEPTIDES

While a majority of dietary peptides are fully digested and absorbed in the small intestine, there is a significant fraction which escapes and reaches the large intestine (a major reservoir of the gut microbes) to either further be digested by microbial enzymes or engulfed by them. As detailed above, there are multiple instances of bacterial absorption of peptides leading to the inhibition of vital microbial pathways and cell death. In the light of this statement, it would be an intriguing thought to evaluate the antimicrobial activity of dietary peptides reaching the large intestine.

Given the the ability of peptides, sharing sequence identity with hot-segments at protein-protein interfaces, to competitively inhibit PPI; we propose an intriguing idea of exploring the interaction of dietary peptides (peptides originating from digestion of dietary proteins in the human gastrointestinal tract) with gut microbes and test if such peptides can be subcategorized as new class of antimicrobial peptides. There are several unfathomed aspects of these putative interactions, such as the optimum length and composition of peptides for microbial absorption or surface binding, minimum inhibitory concentration of peptides, dietary proteins which are a rich source of such bioactive peptides, and finally fast and robust computational protocols to predict bioactive peptides and evaluate their ability to inhibit protein-protein interactions. We hope that with our increasing understanding of the composition of the gut microbiome and its association with human health, there would be significant interest among the scientific community about the interaction of gut microbes and dietary peptides. A natural extension of it would be the targeted dietary peptide based modulation of the gut microbiome to treat metabolic disorders. Authors, part of the current manuscript, are currently performing in vitro experiments to explore the absorption and microbial pathway inhibitory activities, of dietary peptides.

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