War and peace in the human gut: Probing the microbiome

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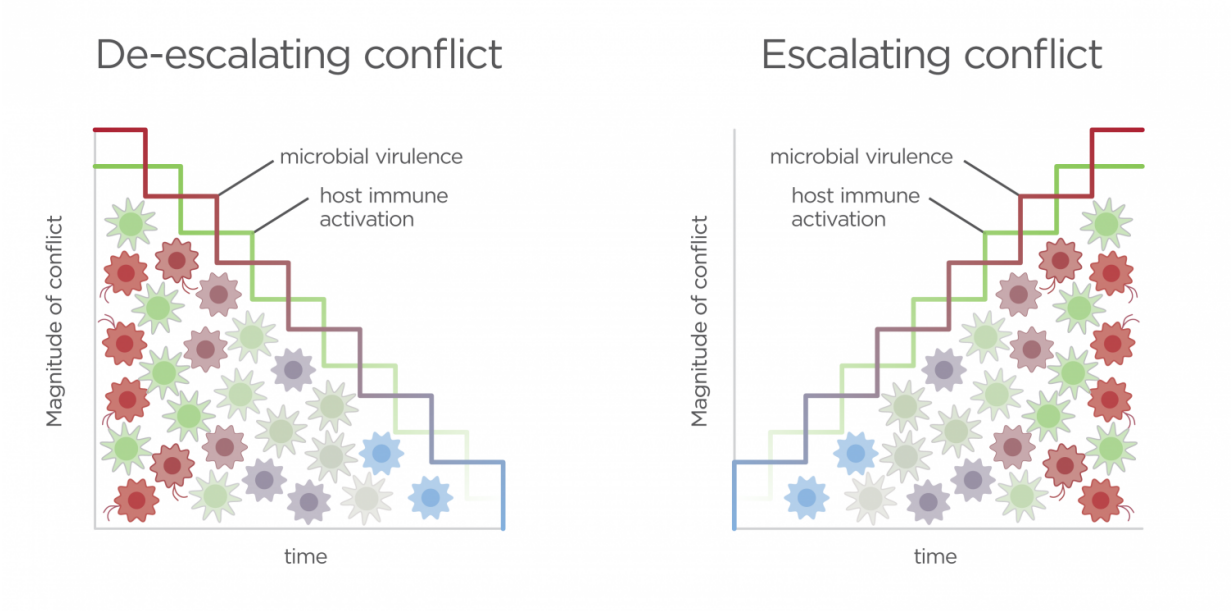


Dangerous escalation may result from unresolved conflict between host and microbiota, fueled by a competitive arms race between host and microbiota. Immune resistance is triggered by microbial signals associated with invasion or other harm to the host. Inflammation, in turn, causes increased microbial virulence gene expression. Positive feedback perpetuating escalating conflict can result in increasing costs and a negative outcome for both partners. Credit: Jason Drees for the Biodesign Institute

Human well being often flourishes under conditions of cooperation with others and flounders during periods of external conflict and strife.

According to Athena Aktipis, a researcher at Arizona State University's Biodesign Institute, microbes within the body—collectively known as the microbiota—also engage in cooperative and combative behavior with human cells in their environment. This is particularly true in the human gut, where many trillions of them exist in the digestive tract in communities of bewildering diversity.

In research appearing in the current issue of *Annals of the New York Academy of Sciences*, Aktipis and her colleagues Helen Wasielewski (ASU's Department of Psychology), and Joe Alcock, (at the University of New Mexico Department of Emergency Medicine), examine the role of microbes in the gut. Their study explores how dietary choices promote cooperation or might fuel conflict between gut microbes and the humans they interact with, maintaining health or encouraging the onset of disease.

The new research provides important insights into the subtle interplay of diet and human health as well as paving the way for management of the microbiome, particularly for the treatment and prevention of inflammatory and metabolic disease.

"Our gut microbes are not just passive recipients of the food that we eat - they evolve and change in response to what we feed our bodies. And there are certain foods that lead to resource sharing between us and our microbes, while other foods can lead to conflict and resource competition between our bodies and our microbes," Aktipis says. "This cooperation and conflict framework can help us understand certain aspects of why we get sick and how we can stay healthy."

Bacterial nation

Scientists are only beginning to appreciate the significance and complexity of the bacteria comprising the microbiota, which number

approximately 30 trillion, about the same number as human cells. Colonization of the body by a vast array of microbes begins at birth, when a newborn is exposed to maternal vaginal, fecal and skin flora.

Most of the human microbiota resides in the gut. At least 500 different species exist, though most fall into several well-recognized groups. Emerging research suggests the composition of these microbes exerts a profound influence on human health throughout life, including the propensity for obesity and the susceptibility to allergies. They may even affect behavior.

In the new manuscript, Aktipis and her colleagues explore the effects of particular nutrients in food on the behavior of gut bacteria. Their innovative approach applies evolutionary theory to the issue and proposes that the microbes inhabiting the human gut engage in competitive or cooperative behavior, depending in part on the particular diet they are exposed to.

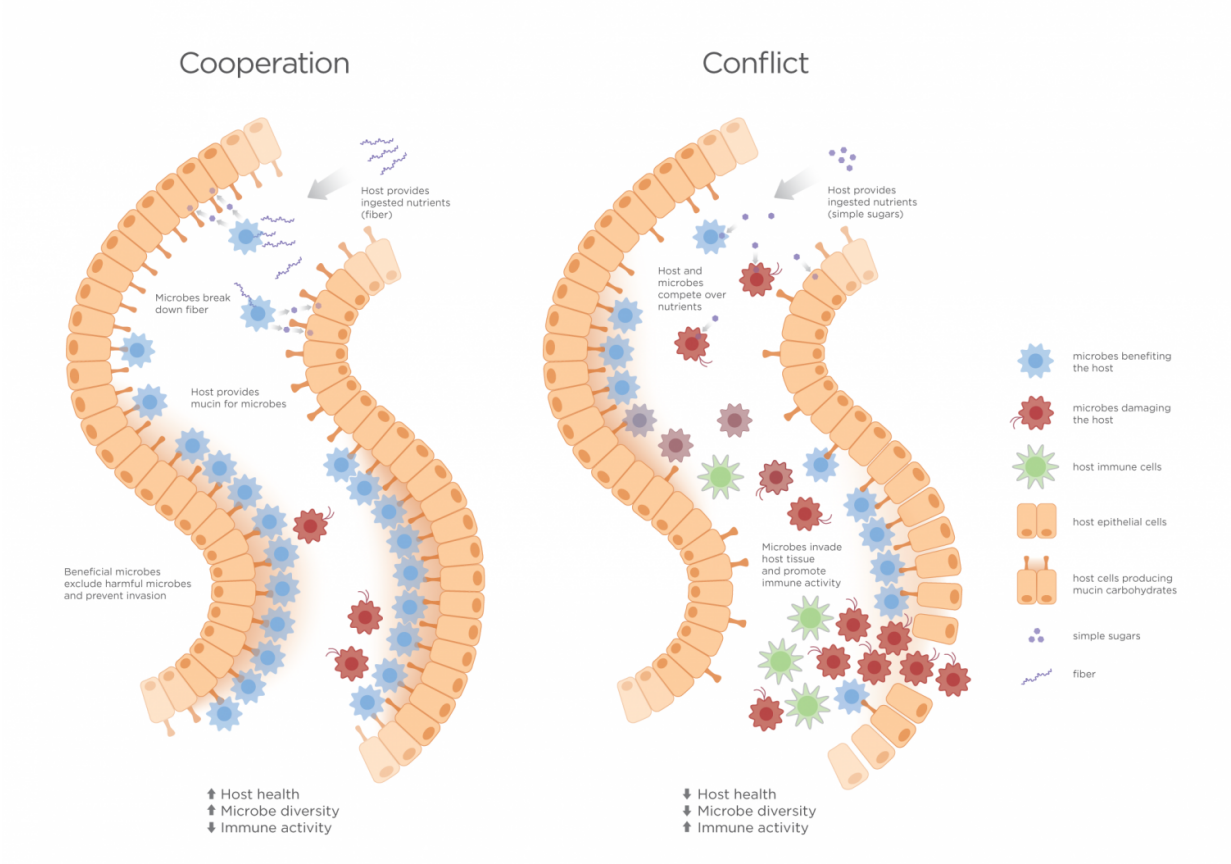
Support vs strife

Cooperation and competition are hallmarks of evolutionary processes, guiding the fate of all living organisms. In the human body, conflict and cooperation between cells of differing genetic makeup can have important consequences for health and disease.

One classic example is that of cancer cells, which mutate genetically, form independent clusters and rob resources from the host for their own benefit. Cell competition can also occur between maternal cells and those of a developing fetus, another topic Aktipis has explored in earlier research.

In the current study, Aktipis and her colleagues examine cooperation and competition between the human and non-human, that is, between the

cells making up human tissues and organs and the multitude of microbes (e.g. bacteria, fungi, and archaeons) co-existing in the same individual.



De-escalation of conflict can reduce costs associated with conflict to both host and microbiota. Host immune tolerance may have evolved as a strategy of managing conflict between host and microbiome, reducing costly host inflammation and microbiota virulence in the microbiome. Credit: Jason Drees for the Biodesign Institute

Cooperative behavior between humans and gut microflora occurs when bacterial cells produce energy and vitamins and help to screen out pathogens threatening the host. In return, host cells help maintain the

microbial habitat, providing them with an environment conducive to their growth and proliferation—a win-win situation.

The authors propose that a cooperative alignment of needs between gut microbes and the human host should lead to positive health outcomes, while conflicts over resource utilization can often generate disease.

Helen Wasielewski, Postdoctoral Scholar in the Aktipis Lab, argues that taking a microbial perspective is useful in understanding these cooperative relationships: "Thinking about transmission, or how these microorganisms move between hosts, is really important here. If bacteria are able to move between hosts easily, they can exploit the current host and move on, whereas if they're more limited they can become dependent upon the reproductive success of the host for their own success," she says. "In extreme cases, symbionts become dependent upon their hosts to such an extent that they no longer have the capacity to live outside the host - we see examples of this in some invertebrates."

Food fight

Internal disputes can break out when the needs of microbes and humans are at cross-purposes. Should conditions of cooperation break down, gut microbiota may contribute to chronic afflictions including inflammatory, metabolic and cardiovascular diseases or use nutrients intended for the host, causing inflammation and other negative health effects.

Sugar and fat in the diet may constitute a recipe for such internal conflict. Unlike dietary fiber, fats and simple sugars can be used not only by host cells but also by potentially harmful microbes, such as pathogenic E. coli. Instead of resource sharing, a microbial tug-of-war ensues.

When low fiber intake in the diet is combined with abundant sugar,

populations of harmful microbes can expand, leading to inflammation-related illness. The ingestion of iron also carries certain health risks and can sometimes lead to internal conflict. A variety of pathogens steal iron directly from host cell proteins. When harmful microbes gain access to key nutrients like iron, the body responds by ramping up immune activity against these microbes. This can result in escalating conflict between human and microbial cells, with deleterious impacts on human health, that may include adipose inflammation, obesity and diabetes.

What's cooking?

In gauging the health effects of modern Western diets, the new study identifies both benefits and risks associated with cooperation and conflict in the human gut.

The wide availability of foods with high nutritional density and low pathogen load acts to promote health through microbe-human cooperation. Among the specific nutrients examined in the study, breast milk is highlighted for its benefits to both mother and infant. It has been credited with reducing infant mortality and limiting the risk of chronic diseases later in life.

Non-digestible carbohydrates in milk feed protective microbiota in the gut. Specialized proteins in breast milk provide an immunological effect, including cytokines, immunoglobulins, and lactoferrin that act to reduce infection risk.

On the other hand, Western diets may contribute to human disease, including obesity and other chronic inflammatory diseases as a consequence of their low fiber content and high proportion of simple sugars, saturated fats and emulsifying agents.

The research findings highlighted in this paper mark a departure from

conventional ideas concerning diet, suggesting the negative health consequences of certain foods may be due to their effects on the subtle interconnection of host and microbiome.

More information: Helen Wasielewski et al, Resource conflict and cooperation between human host and gut microbiota: implications for nutrition and health, *Annals of the New York Academy of Sciences* (2016). DOI: 10.1111/nyas.13118