SATURDAY, November 5, 2022

Canada Future Directions in IBD

SESSION IV

MANIPULATING THE MICROBIOME: NOVEL APPROACHES

The Microbiome in IBD: What makes the gut abnormally inflamed?

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Microbiome-host interactions in the healthy gut maintain a stable and resilient homeostasis. In IBD host genetics, altered microbiota and environment (including diet) contribute to disease risk but with no single cause initiating disease. However, once initiated, multiple microbiome pathways contribute to and maintain intestinal inflammation and extra-intestinal phenotypes. The list of microbiome-derived metabolites that contribute to inflammation is growing.[1] Beneficial metabolites depleted in IBD include short-chain fatty acids, which among other activities, help maintain barrier function. Tryptophan-derived metabolites such as the indole derivatives act through aryl hydrocarbon receptors to modulate immune cell differentiation and function. The microbiome can also alter gut-produced serotonin, which is proinflammatory.[2] Microbiota-encoded enzymes can alter host metabolites and barrier function. Bile salt hydrolases expressed by the microbiome, are critical for normal bile recycling and homeostasis, and are altered in disease.[3] Proteases and carbohydrate active enzymes can degrade mucins and modify host cell surface receptors. Mucous thinning and encroachment of the epithelium by microbiota in the inflamed gut can lead to inflammation through pathogen-associated molecular pattern molecule (PAMP) signaling. The inflamed gut can in turn lead to psychiatric co-morbidities such as stress and anxiety through production of neuroactive metabolites, systemic inflammation (due to decreased barrier function), and activation of efferent nerve activation.[4]

This myriad of pathways that can drive in IBD inflammation may also contribute to heterogeneity in disease and in response to therapy. The diversity, redundancy and yet to be discovered pathways metabolic complexity of the microbiome represent both a challenge and opportunity for microbiome derived therapies in IBD.

References

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