From Microbial Ecology to Malignancy: Exploring the Gut Microbiome Across Haematological Disease

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THE INFLUENCE of the gut microbiome extends far beyond the gastrointestinal tract, with growing evidence linking the gut microbiome to immune regulation, haematopoiesis, ageing, and cancer. During the European Hematology Association's (EHA) session titled 'The Role of the Gut Microbiome in Normal and Malignant Blood Cell Development', experts explored how advances in microbiome research are reshaping understanding of both normal blood cell development and haematological malignancies. Presentations from Hitoshi Takizawa, International Research Center for Medical Sciences, Kumamoto University, Japan; Christina Schjellerup Eickhardt-Dalbøge, Regional Department of Clinical Microbiology at Zealand University Hospital, Denmark; and Ben Boursi, Associate Professor, Faculty of Medicine, Epidemiology & Preventive Medicine, Tel Aviv University, Israel, highlighted the microbiome as both a driver of disease and a promising therapeutic target, with implications spanning basic biology through to cancer treatment.

A DYNAMIC REGULATOR OF BLOOD CELL DEVELOPMENT

Opening the session, Takizawa described the gut microbiome as a dynamic ecosystem that evolves throughout life in response to factors including diet, environment, and ageing.[1] Although the human body harbours an estimated 38 trillion bacteria, he emphasised that their importance lies not simply in their abundance, but in their constant communication with the immune and haematopoietic systems.

Recent research has begun to reveal the mechanisms underpinning this dialogue. Microbiota-derived metabolites, including lipopolysaccharides (LPS), circulate beyond the gut and stimulate cytokine pathways involving Type I interferons, TNF-α, IL-17, and thrombopoietin, ultimately influencing haematopoietic activity within the bone marrow.[2,3] Despite the physical distance between the gut and bone marrow, these signalling molecules provide an important mechanistic link between intestinal homeostasis and blood cell production.[2,3]

Evidence from germ-free and antibiotic-treated mouse models has further demonstrated the microbiome's importance in maintaining healthy haematopoiesis. Germ free animals exhibited reduced numbers of haematopoietic stem and progenitor cells, granulocytes, monocytes, and macrophages, resulting in impaired responses to bacterial infection.[4] Takizawa highlighted studies showing that recolonisation with faecal microbiota, or even transfer of serum from specific pathogen free animals, partially restored bone marrow granulopoiesis, suggesting that circulating microbial metabolites, rather than proteins alone, are key regulators of haemopoietic activity.[5]

The microbiome also plays an important role during inflammation and tissue injury. Experimental disruption of the intestinal barrier allowed microbial products to enter the circulation, stimulating the expansion

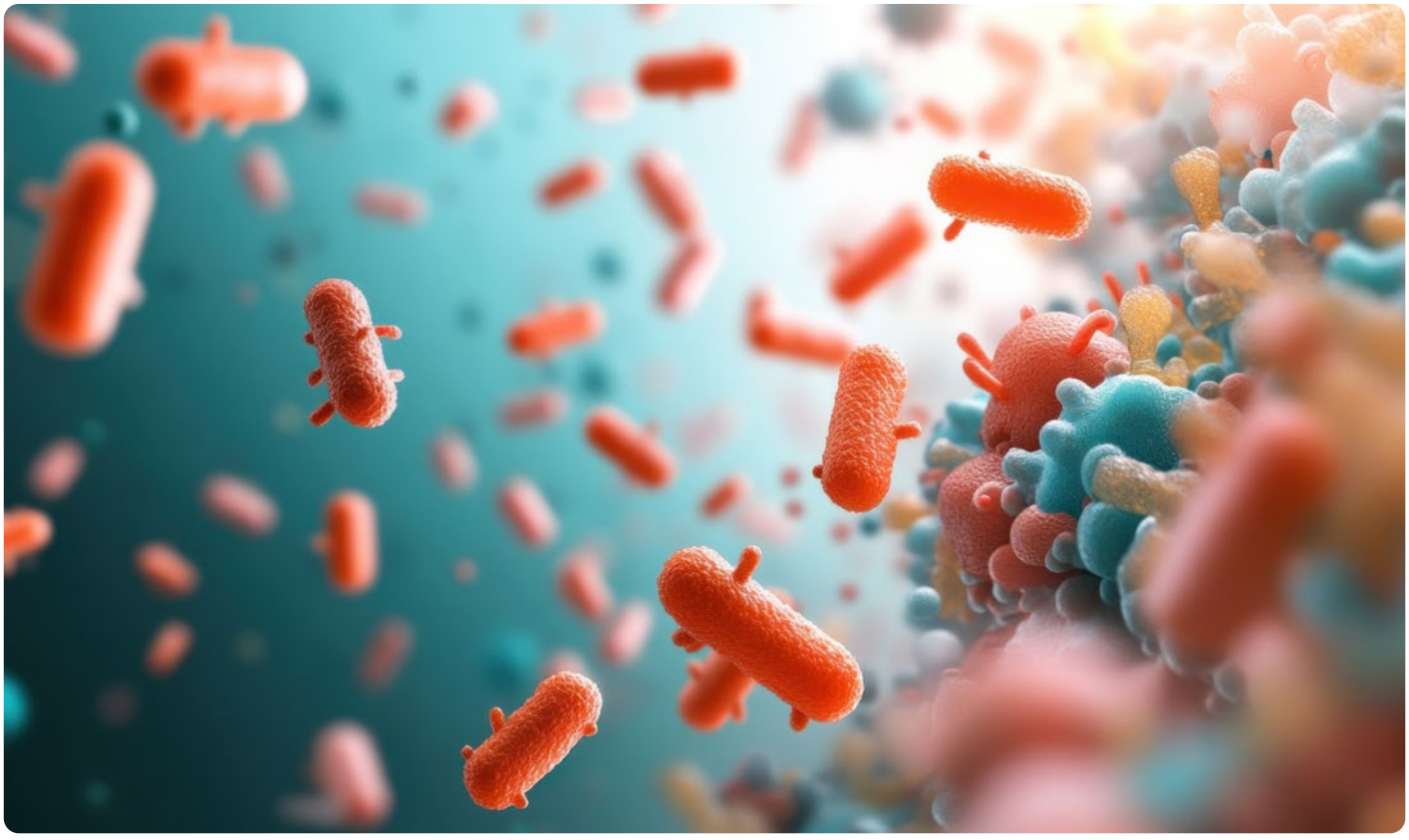
of myeloid progenitors within the bone marrow before their migration to sites of inflammation, where they contributed to tissue repair. Together, these findings illustrated how microbial signals influence not only steady-state blood cell production but also the adaptive response to physiological stress.[6]

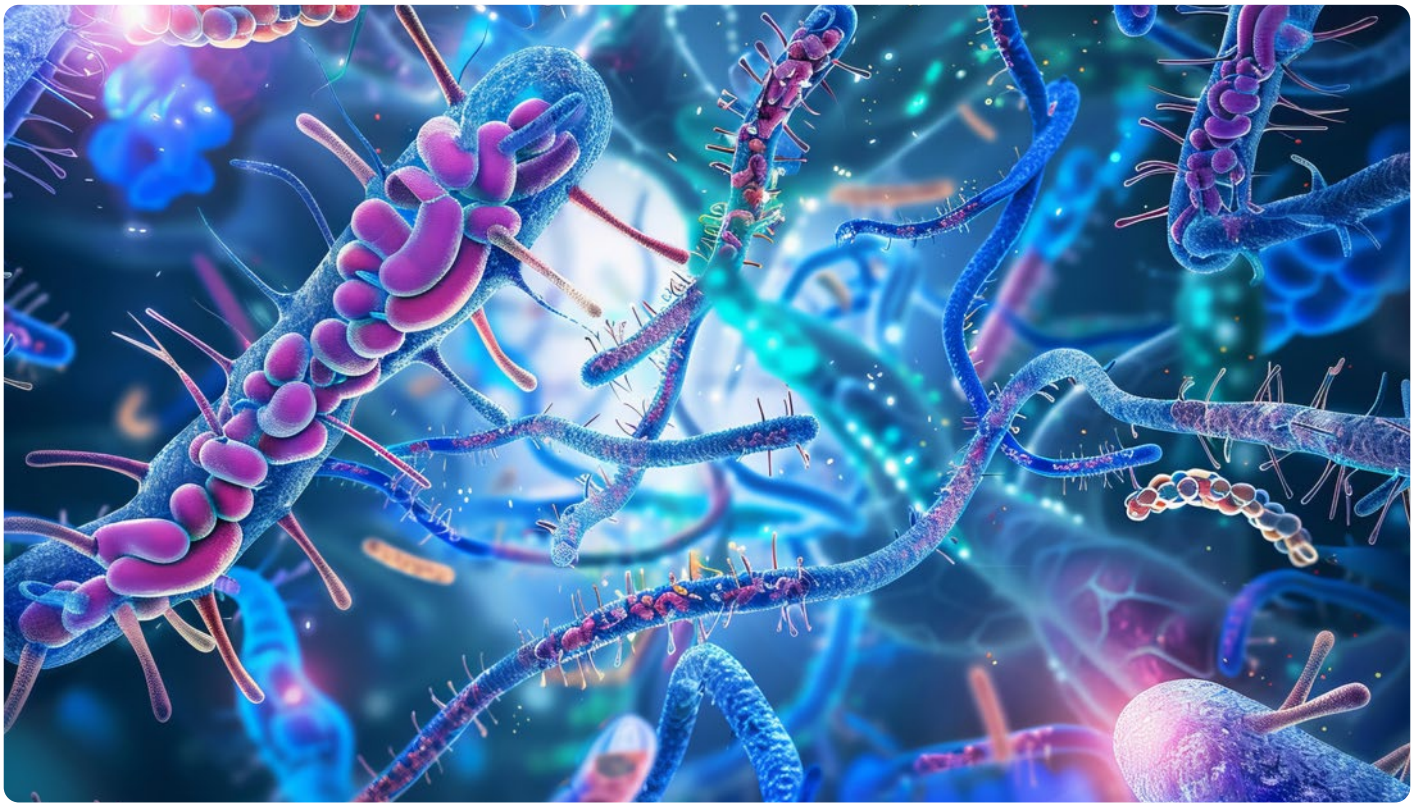
> **Microbial signals influence not only steady-state blood cell production but also the adaptive response to physiological stress**

LINKING THE MICROBIOME WITH AGEING AND CLONAL HAEMATOPOIESEIS

Takizawa went on to explore the relationship between the gut, microbiome, and ageing, proposing that age-related changes in haemopoiesis may be driven, at least in part, by chronic inflammatory signalling originating in the gut. In murine models, inhibition of IL-1 receptor signalling or depletion of microbial stimuli through antibiotic treatment partially restored lymphoid reconstitution in aged animals, suggesting that microbial-derived inflammatory signals contribute to the characteristic shift towards myeloid-biased haematopoiesis observed with ageing.[7]

These observations may also help explain why only a proportion of individuals with age-related clonal haematopoiesis progress to overt haematological malignancy. Takizawa presented emerging evidence identifying the bacterial metabolite ADP-heptose as a potential driver of ageing-related clonal expansion through activation of the ALPK1 signalling pathway.[8] Increased concentrations of ADP-heptose was also reported in patients with inflammatory bowel disease and patients with clonal haemopoiesis, while altered ALPK1 expression has also been observed in myelodysplastic syndromes, supporting the hypothesis that microbial metabolites may directly contribute to malignant evolution.





MICROBIAL DYSBIOSIS IN MPN

Building on these mechanistic insights, Eickhardt-Dalbøge turned her attention to myeloproliferative neoplasms (MPN), describing these disorders as 'a biological continuum', with essential thrombocythaemia, polycythaemia vera, and primary myelofibrosis representing interconnected stages of disease progression rather than entirely discrete, unrelated disease.

Although alterations in the gut microbiome have been reported across several haematological malignancies, including acute myeloid lymphoma and chronic lymphocytic leukaemia, relatively few studies have examined MPNs specifically. Given the central role of chronic inflammation in these disorders, Eickhardt-Dalbøge suggested that this represents an important avenue for future research.

Eickhardt-Dalbøge's group's analyses identified clear differences in microbial diversity between patients with MPN and healthy controls.[9] Patients with essential thrombocythaemia demonstrated increased bacterial richness but reduced abundance of several beneficial taxa, indicating that greater diversity alone does not necessarily reflect a healthier microbial ecosystem. Similar patterns were observed in polycythaemia vera.[9]

Perhaps most notably, microbial composition appeared to correlate more strongly with underlying mutation status than clinical diagnosis. Alterations were most pronounced in patients with *JAK2* mutations, whereas differences associated *CALR* mutations were comparatively modest.[10] Patients with a higher *JAK2* allele burden also exhibited increased abundance of *Akkermansia*.[10] While generally considered a beneficial commensal bacterium, Eickhardt-Dalbøge noted that excessive levels may degrade the intestinal mucus layer and contribute to increased gut permeability, reinforcing the concept that microbial balance, rather than the presence of individual bacterial species, is central to maintaining intestinal health.

Taken together, the first two presentations suggested that intestinal barrier dysfunction, microbial dysbiosis, and chronic inflammation are closely intertwined. Rather than simply reflecting disease, alterations in the gut microbiome may actively shape haematopoiesis and influence the initiation and progression of haematological malignancies.

FROM MECHANISM TO MEDICINE

Concluding the session, Boursi explored how growing understanding of the gut microbiome is beginning to translate novel approaches to cancer treatment. Challenging conventional views of precision oncology, he argued that cancer should not be considered solely a genomic disease, but rather part of a broader ecological system encompassing the tumour, host, immune system, and microbiota. As Boursi remarked: "Today, when we talk about multiomics, we must remember that we are not studying just the tumour, we are studying a dynamic meta-organism."[11]

Reflecting this shift in thinking, the microbiome is now recognised as an emerging hallmark of cancer, influencing tumour development, immune responses, and treatment outcomes.[12] Boursi described how microbes can contribute to tumour formation by inducing DNA damage, activating oncogenic pathways, impairing DNA repair, and promoting chronic inflammation and immunosuppression.[13] He also highlighted growing evidence that the microbiota influences responses to cancer therapies, either enhancing efficacy or contributing to resistance and toxicity.[14-15]

Much of the current research has focused on immunotherapy, where several prospective studies have demonstrated associations between gut microbial composition and response to immune checkpoint inhibitors.[11] While different studies have identified different bacterial species, microbiota transfer experiments have supported a causal relationship, with similar findings also reported in CAR-T cell therapy efficacy.[11] Boursi suggested that these observations have prompted increasing interest in microbiota-directed interventions, including faecal microbiota transplantation, probiotics, prebiotics, postbiotics, and synbiotics. Early clinical evaluation of faecal microbiota transplantation has shown encouraging results, with three of 10 patients with metastatic melanoma unresponsive to at least one line of immunotherapy responding to treatment, including one durable complete response and two durable partial responses.[16]

> **The microbiome is now recognised as an emerging hallmark of cancer**

CONCLUSION

Looking ahead, Boursi emphasised that understanding microbial function, rather than composition alone will be key to translating these discoveries into clinical practice. Approaches such as predictive tools for microbiota engraftment, alongside engineered bacterial therapies and strategies targeting the intestinal barrier, may further refine microbiome-based interventions. Together, the presentations highlighted the gut microbiome as a fundamental regulator of haematopoiesis, immune function, and cancer biology, suggesting that harnessing the host ecosystem could become an important component of future strategies for preventing and treating haematological malignancies.

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