EDITORIAL

Gut microbiota and myeloproliferative neoplasms

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The human gut microbiota refers to the collective assembly of microorganisms inhabiting and colonizing the gastrointestinal tract, including bacteria, archaea, and eukarya.[1] This intricate microbial ecosystem exists in a symbiotic relationship with the host, with trillions of microorganisms playing key roles in maintaining human health.[2] *Firmicutes* and *Bacteroidetes* represent the predominant bacterial phyla that form the intestinal microbiome.[2] The gut microbiota has developed adaptive mechanisms to promote its survival within the gastrointestinal tract. Development of the intestinal microbiome has been depicted and seems to be influenced by a variety of factors, e.g., mode of delivery, diet during infancy and adulthood, illnesses, and antibiotic treatment causing variation in the composition of the microbiota.[3] Before the age of three, children's intestinal microbiome already resembles the gut microbiota of adult individuals in terms of functional capabilities, diversity, and composition.[4] The gut microbiota offers numerous benefits to the host as its metabolic activity is responsible for the generation of short-chain fatty acids which are a source of energy for the host, and for the fermentation of carbohydrates leading to the synthesis of oxalates, reducing the risk of oxalate stones in the kidney.[5] In addition, the microbiota promotes lipid metabolism, vitamin synthesis, polyphenol breakdown, drug metabolism, immunomodulation, which offers immune-protection, and maintains the structural integrity of the gastrointestinal tract.[3] Therefore, the gut microbiota represents an intricate microbial ecosystem that plays a critical role in maintaining human health.

Myeloproliferative neoplasms (MPNs) are a group of haematological disorders characterized by the clonal proliferation of one or two myeloid lineages. Classical, Philadelphia-negative MPNs include polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF).[6] Inflammation is a central contributor to the pathogenesis of MPNs, and gut microbial dysbiosis, which refers to the disruption of the composition of the microbial communities that normally reside in the gut, has been implicated in the pathobiology of haematologic malignancies.[7] Janus kinase (JAK) mutations are commonly found in MPNs, with *JAK2V617F* being the most frequent genetic alteration discovered, being present in about 95% and 50-60% of the subjects diagnosed with PV and of the subjects suffering from ET and PMF, respectively.[11] Inflammation creates a favourable environment for the growth of *JAK2V617F*-mutant haematopoietic stem cells which then develop resistance.[7] *JAK2V617F* further induces inflammation by producing pro--inflammatory cytokines/chemokines, e.g., interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α).[7] Moreover, aging is regarded as a pro-inflammatory state and has been linked elevated concentrations of pro-inflammatory cytokines.[7] Therefore, the inflammatory state in aging individuals may contribute to the development of MPNs.

An investigation by Oliver et al highlights that there are notable differences in the gut microbiota of MPN patients versus healthy individuals. The study detected no key differences in the diversity of the gut microbiome between subjects diagnosed with MPNs and healthy comparators. However, a random forest model distinguished between the two groups based on microbiome composition. An operational taxonomic unit from the genus *Phascolarcobacterium* was found to be significantly lower in MPNs versus the control group. *Phascolarcobacterium* has been highlighted to confer protective benefits against *Clostridium difficile* infection. A decrease in the amount of *Phascolarcobacterium* is observed in ulcerative colitis and primary sclerosing cholangitis. Moreover, the depletion *Phascolarcobacterium* has been associated with the depletion of intestinal short chain fatty acid propionate. Since in autoimmune disorders there is a reduced *Phascolarctobacterium* abundance, this phenomenon suggests that *Phascolarctobacterium* could potentially play a role in modulating inflammation.

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Nevertheless, one must take into consideration that the conclusions of the research were based on the assessment of a small number of subjects, hence, future investigations are required to validate the aforementioned findings and clarify the potential implications of the gut microbiome in MPN pathogenesis.[8]

In another study, that compared subjects diagnosed with PV versus healthy individuals, the former displayed significantly lower alpha diversity but higher richness of gut microbiota. This study also found differences in the bacterial taxa between the two groups. Patients with PV had decreased amount of the phylum *Firmicutes (Ruminococcaceae and Clostridia*) and *Prevotellaceae* (phylum *Bacteroidota*) while there was a notable abundance of the genus *Bacteroides* (phylum *Bacteroidota*) compared to healthy controls. Moreover, patients with PV were divided into four subsamples based on the selection of therapy: no treatment besides low-dose aspirin and phlebotomy, treatment with hydroxyurea (HU), treatment with interferon (IFN), and treatment with a combination of therapies (COMBI). Subjects put on IFN regimens exhibited higher relative abundances of *Firmicutes* and lower abundance of *Bacteroides* compared to patients who were not pharmacological agents. Individuals who were prescribed COMBI displayed elevated relative abundances of *Bacteroides* and lower abundance of *Firmicutes* compared to those who received IFN. To put it into a nutshell, there were differences in the relative abundance of certain taxa between treatment groups.[9]

A study by Barone et al investigated the characteristics of circulating extracellular vesicles (EVs) in patients with PV. It was found that PV patients had significantly decreased levels of megakaryocyte (MK) EVs and increased levels of platelet derived (PLT) EVs. Isolated EVs from individuals suffering from PV were notably smaller in size versus healthy donors though both had the same shape as revealed by transmission election microscope. Microbial DNA of isolated EVs showed that PV subjects experienced depletion of *Proteobacteria*-related DNA and enrichment of *Actinobacteria* and *Cyanobacteria*-related DNA. Subjects with PV had higher proportions of EVs associated with lipopolysaccharide compared to healthy donors suggesting increased intestinal permeability and the potential involvement of microbial factors in mediating inflammatory responses in PV. However, analysis of faecal samples revealed no significant microbiome composition between the two groups. The findings suggest that circulating EVs display an abnormal profile in subjects with PV, e.g., altered levels of MK-EVs and PLT-EVs, dysbiosis in EV-associated microbial DNA, and abundance in LPS-associated EVs. These results provide insights into the potential role of EVs and their microbial cargo in the pathogenesis of PV and highlight the importance of the microenvironment in the disease.[10]

A study by Morales and Ferrer-Marin links the clonal evolution of MPNs to certain intrinsic and extrinsic factors. Mutations has been shown in genes such as *JAK2, MPL* and *CALR*. Besides classical driver mutations, additional genetic alterations in genes that partake in the processes of DNA methylation, mRNA splicing, and signaling pathways contribute to the MPN phenotype. Mutations in genes such as *TET2, DNMT3A, ASXL1, EZH2, CBL, SF3B1, PPM1D, NFE2, SRSF2, TP53,* and *U2AF1* are frequently observed. Genetic alterations in genes which partake in DNA methylation, e.g., *ASXL1*, *TET2,* and *DNMT3A*, attribute a proliferative and survival advantage and are associated with clonal haematopoiesis. In MPNs, genetic alterations in splicing factors, e.g., *SRSF2, U2AF1,* and *SF3B1* rank second in terms of frequency amongst the mutated gene categories, particularly in PMF, and are associated with a higher risk of progression/evolution to acute myeloid leukaemia (AML) and poorer survival. Genetic changes in genes involved in DNA repair and other signalling pathways, i.e., *NRAS, PPM1D,* and *TP53,* are also linked to leukaemic transformation and poor prognosis. Furthermore, extrinsic factors, e.g., environmental exposure and microbiota, to name a few, play important roles in the evolution of MPNs.[11]

In conclusion, the human gut microbiota is important for maintaining health, but its disturbance, known as dysbiosis, has been linked to haematologic malignancies like MPNs. Further research is needed for a better understanding of the involvement of intestinal microbiome in haematologic malignancies and the discovery of effective treatments.

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