Cachexia during anti-leukemia chemotherapy: it is not "just" the chemo

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Usually, acute myeloid leukemia (AML) arrives suddenly and is rapidly fatal, if left untreated. The patient has typically not heard of their disease before, and at diagnosis often has no choice but to quickly prepare for the worst. The move from that point on is normally so fast that the initial pre-chemotherapy discussions are largely limited to the risks of death, relapse, infection, and bleeding. Some days later, when the patient stops eating and starts to lose weight, we place a nasogastric tube or initiate parenteral nutrition. By the time the patient is ready to leave the hospital (i.e., 4 weeks after starting intensive chemotherapy in most centers), they usually look like a different person, casually speaking "beaten up" or more scientifically, "cachectic." Cachexia is a multifactorial systemic syndrome that includes anorexia, muscle wasting, weight loss, inflammation, and varying degrees of insulin resistance. Looking back at the hospital stay, when the family asked in week 2 why their loved one was not eating and/or losing weight, we probably said, "it's just the chemo" or "it's the cancer." In reality, however, we simply did not know.

Pötgens *et al.* tried to address this knowledge gap.[1] They asked whether changes in the gut microbiota (a.k.a. dysbiosis) may have something to do with AML/chemotherapy-associated cachexia. Specifically, could dysbiosis lead to systemic metabolic alterations that in turn cause cachexia? The question was inspired by several prior reports of gut microbiota alterations in AML and their associations with treatment complications, including neutropenic fever and infection.[2] The authors had previously reported on a mouse model of acute leukemia-associated cachexia in which a synbiotic ameliorated gut dysbiosis, reduced cachexia, and improved survival.[3] The contribution of the gut microbiota to circulating metabolites has been established,[4] making the authors' hypothesis mechanistically plausible.

Pötgens *et al.* enrolled 30 newly diagnosed AML patients and matched them 1:1 with healthy controls for age, sex, body mass index, and smoking status. Lack of antibiotic exposure for 30 days before sampling the baseline (pre-chemotherapy) gut microbiota ensured a true baseline sample. This was a major advantage in the authors' analyses because the urgency of treatment and universality of antibiotic prophylaxis make it difficult to secure true baseline samples. The multi-omics analyses included microbiota profiling (short-amplicon and shotgun metagenomic sequencing of stool), metabolomics (stool, blood, and urine), clinical measurements (body composition, muscle strength, appetite, diet, and weight), and laboratory assessments (cytokines and insulin resistance).

Importantly, AML patients and their matched controls had similar anthropometric characteristics and life habits. However, AML patients displayed muscle weakness, anorexia, insulin resistance, and signs of oxidative stress and systemic inflammation. The gut microbiota in these patients showed an expansion of bacteria that are typically of oral origin, and a shrinkage of obligate anaerobes. Importantly, numerous significant associations were found between the gut microbiota and clinical/laboratory markers of cachexia, including altered redox status, inflammation, insulin resistance, muscle weakness, and anorexia.

Although the specific taxa and biomarkers with significant associations in the study by Pötgens *et al.* need validation in larger cohorts, the supported concepts nicely connect with some prior work and expand the current perspective to the symptomatology of AML and its treatment. For example, oxidative stress was shown in a previous study to potentially mediate the association between dysbiosis, specifically expansion of the mucolytic genus *Akkermansia*, and neutropenic fever during AML induction chemotherapy.[5] The findings of Pötgens *et al*. suggest that the implications of microbiota-induced oxidative stress go beyond fever and may extend to cachexia, potentially explaining the long-known association between cancer cachexia and fever.[6] Similarly, the expansion of typically oral bacteria in the baseline stool samples of AML patients suggests ectopic

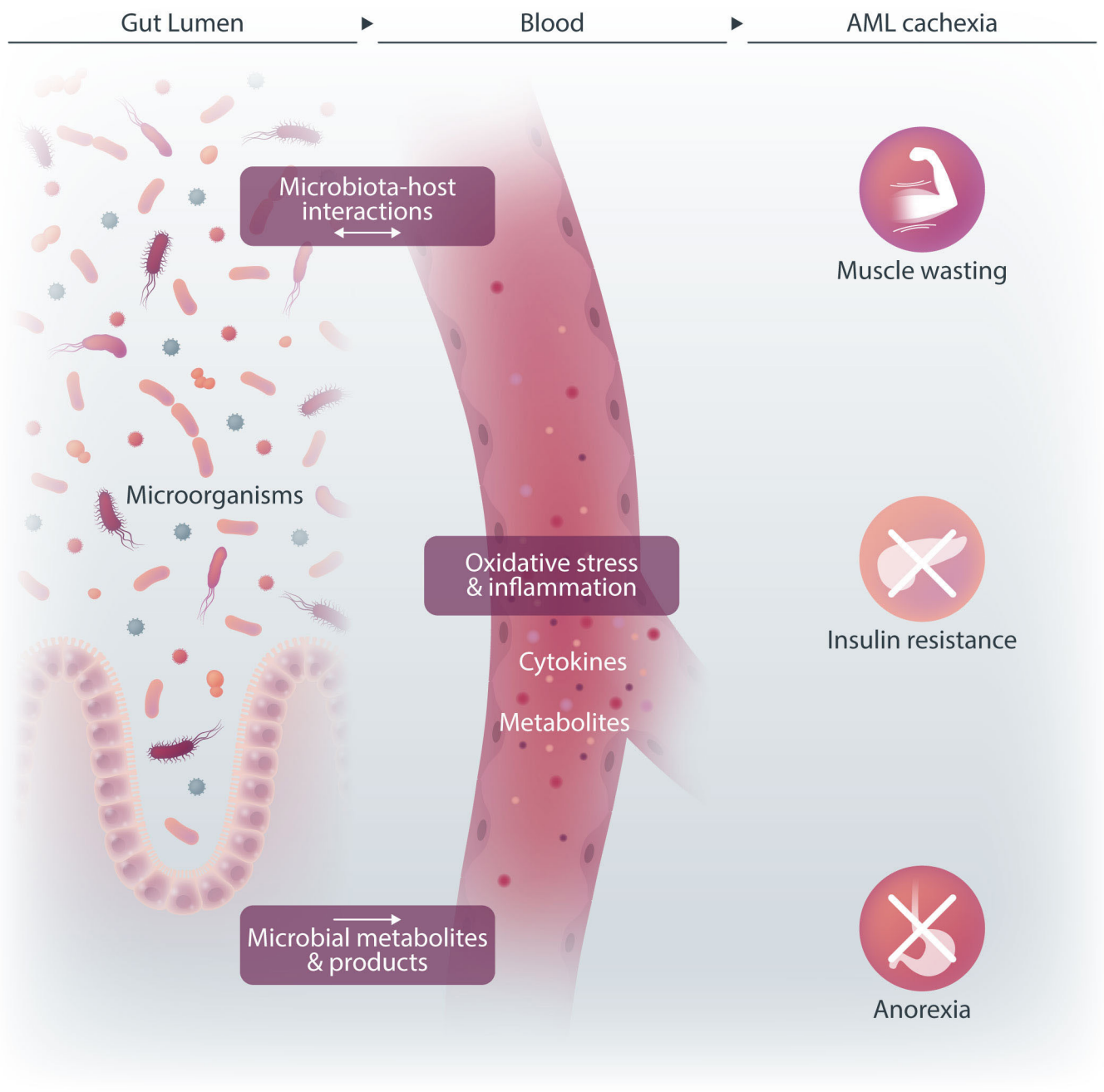

Figure 1. The proposed connection between the gut microbiota and cachexia in patients with acute myeloid leukemia. Patients with acute myeloid leukemia (AML) exhibit changes in their gut microbiota, some of which may have begun even before any exposure to antibiotics or chemotherapy. Microbiota effects may occur because of direct physical interactions between microorganisms and intestinal epithelium (or mucosal immune system) or be mediated by microbial products. These pathways can alter the circulating metabolome and proteome, leading to inflammation and oxidative stress, among other effects. Clinical phenotypes associated with these changes that are frequently seen in AML patients include muscle wasting, anorexia, and insulin resistance, collectively manifesting as cachexia.

colonization of oral bacteria in the gut. While an overlap between oral and colonic flora was shown to occur during AML induction chemotherapy in another recent study,[7] Pötgens *et al*. show that this overlap may be present even before exposure to chemotherapy or antibiotics. Ectopic colonization of oral bacteria in the gut almost never occurs in healthy adults,[8] and may thus be a disease hallmark, with potential clinical consequences. A breakdown of the oral/colonic microbiota segregation in common diseases, such as inflammatory bowel disease and colon cancer,[9,10] suggests that oral bacteria may become pathogenic if they reach and survive in the colon.

The report by Pötgens *et al*. represents the first comprehensive attempt to understand how gut microbiota may contribute to AML-related cachexia (Figure 1). It is an important segue to future validation studies in larger cohorts and to mechanistic research. Such studies could eventually lead to microbiota-directed interventions to prevent and treat cachexia in patients with AML or other cancers. For now, when we are asked "Why is my brother with AML losing appetite, muscle, and weight?", the right answer is probably not "It's just the chemo".

Disclosures

AR receives consulting fees from Seres Therapeutics, Ltd. and serves as a member of an Emmes Data and Safety Monitoring Board, neither of which is relevant to this invited editorial.

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