Editorial

Gut microbial-induced inflammation: normal aging or lifestyle changes?

Hein M. Tun, Brittany A. Matenchuk, Anita L. Kozyrskyj

Department of Pediatrics, University of Alberta, Edmonton, AB, Canada

Correspondence to: Anita L. Kozyrskyj, PhD. Department of Pediatrics, University of Alberta, 3-527 Edmonton Clinic Health Academy, 11405-87th Avenue, Edmonton, AB, T6G IC9, Canada. Email: kozyrsky@ualberta.ca.

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Driven by an imbalance between inflammatory and anti-inflammatory networks, the inflammaging phenotype is a state of low-grade chronic inflammation. It has been hypothesized but not confirmed that aged-related tissue 'wear and tear' elevates levels of pro-inflammatory cytokines. Enter the forgotten organ, the gut microbiome, and recent reports of correlations between gut microbial composition and circulating levels of cytokines in nursing home elderly. As with all cross-sectional studies, one cannot determine whether gut microbiota were the drivers or consequence of age-associated inflammation in the Claesson *et al.* study (1). Experimental studies on knockout (KO) mice such as the one published by Thevaranjan *et al.* (2), are required to test the temporality question. This will be the focus of our editorial, appreciating the fact that Thevaranjan *et al.* also reported on the reduced ability of macrophages to kill Streptococcus pneumonia and mount a pro-inflammatory interleukin-6 (IL-6) response with advanced age and in the presence of tumor necrosis factor-α (TNF-α); an absence of the latter cytokine in TNF-KO mice reversed age-associated increases to IL-6 levels and impaired macrophage killing of *S. pneumonia* (2).

Although higher TNF-α levels in adults predict mortality, evidence for whether they are elevated in the elderly versus younger adults is conflicting (3-7). Thevaranjan *et al.* nicely established a link between quantity of circulating TNF-α and the 'age' of microbiota in fecal transplant studies of germ-free mice, showing that age of microbiota and not age of the host may be relevant to TNF-α (2). Their finding that TNF-α levels were highest in old germ-free mice colonized with old, as well as young specific pathogen-free (SPF) microbiota, suggests that an "old" host can influence "young" microbiota. Next, based on 16S rRNA Illumina sequencing of the hypervariable V3 region, Thevaranjan *et al.* confirmed that age-related microbial dysbiosis was not present in TNF-KO mice (2). Shown to be elevated in old *vs.* young wild type mice but not in old *vs.* young TNF KO mice were genus *Ruminococcus*, *Clostridium*, *Oscillospira* and *Adlercreutzia*, and the *Peptococcaceae* and *Coriobacteriaceae*. We were unable to find reported comparisons of old *vs.* old TNF-KO or young *vs.* young TNF-KO to tease apart TNF-α from age-related effects on gut microbiota.

Taking advantage of an existing treatment for severe arthritis, Humira, Thevaranjan *et al.* repeated their experiments with this anti-TNF-α biologic to find similar changes to gut microbiota for *Adlercreutzia*, *Peptococcaceae* and *Coriobacteriaceae* but none for *Ruminococcus*, *Clostridium* and *Oscillospira* (2). The abundance of fecal *Bacteroides* was decreased by anti-TNF treatment and not by the absence of TNF-α in the KO model. Further, anti-TNF treatment did not alter intestinal permeability. Both young and old germ-free mice colonized with old SPF mouse microbiota exhibited greater gut permeability, as did old GF mice colonized with microbiota from young SPF mice. Old TNF-KO mice did not manifest this intestinal leakiness compared to young TNF-KO, young SPF, or young/old GF mice. Based on these findings, Thevaranjan *et al.* conclude that reducing TNF-α levels rescues microbiota changes and protects old mice from intestinal permeability but their explanation seems to depend on the complete absence of

TNF-α rather than reduced TNF-α levels or activity.

Let us take this opportunity to re-examine the motivating human evidence for animal model studies of inflammaging-related to gut microbiota. A wide range of lifestyle, health and social factors can contribute to gut microbial changes in the elderly, including smoking, depression, subclinical disorders such as atherosclerosis and asymptomatic bacteriuria, and higher adiposity, which also have been associated with higher levels of TNF-α and IL-6 (5,8-10). The elderly living in nursing homes are not healthy active seniors, and have modified activity, diet and sleep patterns, factors known to affect TNF-α levels, as well as gut microbial composition (1,4,11-13). It is conceivable that activity, sleep and diet-related pathways to inflammaging are compounded in nursing home residents. Closer examination of the Claesson *et al.* paper shows that TNF-α associations with gut microbial composition were not seen separately within nursing home residents or their community-dweller counterparts, but within a distinct cluster of elderly persons (many of which resided in nursing homes) with lower body weight and food diversity.

One approach to better understanding inflammaging is to juxtapose the study of the immune system and gut microbial composition in older age versus the first few years of life. Excessive inflammation is a characteristic of the young and the old, as are lower gut microbial diversity and higher relative levels of *Proteobacteria* (14,15). While inflammation is a normal host response to pathogens in early life, the overproduction of inflammatory cytokines may lead to immune-related diseases. For example, the TNF-α response to *Mycobacterium* tuberculosis heightens with advancing infant age (16), yet Halonen *et al.* found elevated levels of LPS-induced TNF-α at 3 months to pose a greater risk for asthma (17). Of note, both age groups have elevated levels of anti-inflammatory cytokines such as IL-10 (15). Thus, healthy aging may also be a function of more efficient anti-inflammatory networks, which also require consideration in experimental models.

We would be amiss in ending our discussion without commenting on a result that caught our attention. One set of gut microbial changes observed in older versus younger mice but not in the presence of a TNF-KO, was the higher abundance of genus *Oscillospira* and *Ruminococcus*. We found the same increases in abundance to these species in our human infant study following prenatal exposure to household pets (18). Leanness is a feature of higher fecal levels of *Oscillospira* in several animal species (19). Could the TNF-α dependent biomarkers of aging reported by Thevaranjan *et al.* be simply a marker of lower body weight in older mice, as it is in the frail elderly?

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