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Reply to the comments by Lu and Hi

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To the Editor

We would like to thank Drs. Lu and He for their comments regarding the potential role of the gut-brain axis (GBA) in the pathogenesis of psoriatic arthritis (PsA). As they correctly point out, a perturbation in the intestinal microbial composition (dysbiosis) can lead to an altered equilibrium in the lamina propria's immune response followed by systemic inflammatory downstream events at distal sites. This has been demonstrated in multiple animal models of autoimmune disease, including those with RA-like phenotype (e.g., K/BxN serum transfer model, IL-1rn−/− and CIA)[1–3] as well as models resembling spondyloarthropaties and PsA (e.g, HLA-B27 transgenic rats and the ZAP-70 single-point mutation SKG mice)[4,5]. For these phenotypes to become clinically evident, most models require the presence of microbes (or their metabolic byproducts), as animals raised under germ-free conditions typically do not develop disease features. Some correlative studies have also shown an association between dysbiotic states and human disease, including inflammatory bowel disease (IBD)[6], rheumatoid arthritis[7], PsA[8] and psoriasis (PsO)[9].

The most compelling argument for GBA involvement in autoimmune disease, however, comes from the multiple sclerosis and neurodevelopmental literature. Taking advantage of the experimental autoimmune encephalomyelitis (EAE), an animal model for multiple sclerosis, several groups have demonstrated that both *Bacteroides fragilis* and a specific metabolite (polysaccharide A) can protect against central nervous system demyelination and inflammation though activation of regulatory T cells (Treg)[10]. This same species also corrects gut permeability, alters microbial composition, and ameliorates autism-like defects in a predisposed model[11].

Although GBA may hypothetically be involved in the development of PsA, a mechanistic explanatory approach will be further required. There are several clues that implicate the intestinal mucosa and the central/peripheral nervous system in the pathogenesis of PsO and

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PsA. First, it is now well established that PsA patients have an increased risk for IBD development and a high prevalence of subclinical gut inflammation[12–14]. Second, multiple lines of evidence described a significant direct correlation between PsO/PsA and anxiety, depression and other neuropsychiatric manifestations[15,16]. Finally, recent elegant studies indicate that specific skin nociceptive sensory neurons, by interacting with local dendritic cells, regulate the IL-23/IL-17 pathway and control cutaneous immune responses in psoriasis-like disease[17]. Whether or not these elements represent a continuum in a yet unidentified biological connection to PsO/PsA pathogenesis remains to be elucidated and proven.

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