Methods Intact female and male, or castrated and sham-castrated male BWF1 mice were used in this study. Cecal contents (microbiota) from different groups were transferred into female BWF1 mice shortly after weaning (~26 days) and either disease or in vitro cell function (cell culture, flow cytometry) was evaluated. Feces were collected from adult mice and analyzed for either microbiota composition (deep sequencing of 16S gene) or metabolomic profiles (mass spectrometry).

Results We have found that the composition of gut microbiota and metabolomic/lipidomic profiles differ between mature female and male BWF1 mice. Transfer of male microbiota to female BWF1 mice suppresses disease and increases survival. Further, we found that male microbiota may protect, in part, via an effect on tolerogenic CD103⁺ dendritic cells (CD103DC) that induce peripheral Tregs (pTregs) through TGfβ and retinoic acid (RA) production. Female BWF1 CD103DC have a decreased ability to induce pTregs and express retinaldehyde dehydrogenase, (RALDH2), an enzyme involved in RA synthesis. Transfer of male microbiota to female BWF1 mice reconstitutes both RALDH2 expression and the ability of the CD103DC to induce pTregs. Interestingly, castration of male mice significantly alters gut microbiota composition and metabolomic/lipidomic profiles by comparison to males, diminishes CD103DC function and decreases the ability of the microbiota to protect female mice from disease. The mechanisms underlying male microbiota-mediated protection from disease are unknown, but may be mediated through the production of metabolites. We have identified several metabolites that are increased in male compared to both female and castrated male feces that function as retinoid X receptor agonists and enhance RALDH2 activity and increase pTregs in vivo.

Conclusions Our data suggest that androgens alter the composition and function of the gut microbiota in males, and the metabolites produced by the male microbiota may have potential for development into therapeutic strategies for the treatment of disease.

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