Biassing of the outcome of antigen (Ag) presentation by calcitonin gene-related peptide (CGRP)-expressed endothelial cells (ECs) requires CGRP-induced expression of chemokine receptors on Ag-presenting DCs. Punna et al. Department of Dermatology, University of California San Francisco, San Francisco, California, United States The gut and skin are major barrier sites that house microbial communities capable of inflaming host tissue, under immunomodulatory conditions, resident and pathogenic microbes are thought to have a dominant impact on local immune cell function. However, the prevalence of neutrophilic skin disorders among patients with IBD suggests that this compartmentalized control may not hold under disease conditions. We hypothesize that an altered immune response to gut-resident bacteria may be responsible for excessive inflammation directed at skin commensals. Our lab has previously shown that colonization of neonatal mice with Staphylococcus epidermidis engineered to express the model antigen 2W (S. epi-2W) results in establishment of antigen-specific tolerance. This tolerance is heralded by a higher percentage of 2W-specific regulatory T cells (Tregs) in the skin and skin-draining lymph nodes (SDLNs) and fewer skin neutrophils upon later-life skin barrier disruption plus S. epi-2W re-exposure. To test whether colitis perturbs tolerance to commensal skin bacteria, we colonized mice with S. epi-2W, challenged them with Staphylococcus aureus (S. aureus) for 5 days, and then subjected them to tape-stripping and S. epi-2W re-exposure. Colitis mice exhibited increased skin neutrophils and reduced percentages of S. epi-specific Tregs in skin and SDLNs compared to controls. Notably, no difference in S. epi-specific Tregs was noted in mice subjected to LPS-induced sepsis, suggesting that gut inflammation specifically was needed. Intra-intestinal presence of S. epi-2W and reduced percentages of S. epi-specific Tregs in the colon and gut-draining SDLNs during colitis indicate initiation of this anti-inflammatory process in the gut. Consistent with this, adoptive transfer experiments revealed a colitis-induced increase in CD4+ T cell trafficking from gut-draining LN to SDLNs. Recovery of S. epi-specific Tregs in colitic C57Bl/6Tg(Rag2-/-) mice indicates an additional role for circulating IL-1 cytokines in shaping the skin commensal response during colitis.