Enterococcus faecalis exploits the human fibrinolytic system to drive excess collagenolysis: implications in gut healing and identification of druggable targets.

Abstract
Perforations, anastomotic leak, and subsequent intra-abdominal sepsis are among the most common and feared complications of invasive interventions in the colon and remaining intestinal tract. During physiological healing, tissue protease activity is finely orchestrated to maintain the strength and integrity of the submucosa collagen layer in the wound. We (Shogan, BD et al. Sci Trans Med 7: 288ra68, 2015.) have previously demonstrated in both mice and humans that the commensal microbe Enterococcus faecalis selectively colonizes wounded colonic tissues and disrupts the healing process by amplifying collagenolytic matrix-metalloprotease activity toward excessive degradation. Here, we demonstrate for the first time, to our knowledge, a novel collagenolytic virulence mechanism by which E. faecalis is able to bind and locally activate the human fibrinolytic protease plasminogen (PLG), a protein present in high concentrations in healing colonic tissue. E. faecalis-mediated PLG activation leads to supraphysiological collagen degradation; in this study, we demonstrate this concept both in vitro and in vivo. This pathoadaptive response can be mitigated with the PLG inhibitor tranexamic acid (TXA) in a fashion that prevents clinically significant complications in validated murine models of both E. faecalis- and Pseudomonas aeruginosa-mediated colonic perforation. TXA has a proven clinical safety record and is Food and Drug Administration approved for topical application in invasive procedures, albeit for the prevention of bleeding rather than infection. As such, the novel pharmacological effect described in this study may be translatable to clinical trials for the prevention of infectious complications in colonic healing.NEW & NOTEWORTHY This paper presents a novel mechanism for virulence in a commensal gut microbe that exploits the human fibrinolytic system and its principle protease, plasminogen. This mechanism is targetable by safe and effective nonantibiotic small molecules for the prevention of infectious complications in the healing gut.

PMID: 31604031 [PubMed - in process]