Thrombin modifies growth, proliferation and apoptosis of human colon organoids: a PAR1- and PAR4-dependent mechanism

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Background and purpose- Thrombin is massively released upon tissue damage associated with bleeding or chronic inflammation. The question of the effects of such thrombin on tissue regrowth and repair has been scarcely addressed, and only in cancer cell lines. The purpose of the present study was to determine thrombin's pharmacological effects on human intestinal epithelium growth, proliferation and apoptosis, using 3-dimentional cultures of human colon organoids.

Experimental design- Crypts were isolated from human colonic resections and cultured for 6 days, forming human colon organoids. Cultured organoids were exposed to 10 and 50 mUmL⁻¹ of thrombin, in the presence or not of Protease-Activated Receptor (PAR) antagonists. Organoid morphology, metabolism, proliferation and apoptosis were followed.

Key results- Thrombin favored organoid maturation leading to a decreased number of immature cystic structures and a concomitant increased number of larger structures releasing cell debris and apoptotic cells. Size of budding structures, metabolic activity and proliferation were significantly reduced in organoid cultures exposed to thrombin, while apoptosis was dramatically increased. Both PAR1 and PAR4 antagonists inhibited apoptosis regardless of thrombin doses. Thrombin-induced inhibition of proliferation and metabolic activity were reversed by PAR4 antagonist for thrombin's lowest dose and by PAR1 antagonist for thrombin's highest dose.

Conclusion and implications- Overall, our data suggest that the presence of thrombin in the vicinity of human colon epithelial cells favors their maturation at the expense of their regenerative capacities. Our data point to thrombin and its two receptors PAR1 and PAR4, as potential molecular targets for epithelial repair therapies.