

## GREMI Thesis Prize 2012 ex-aequo

### Role of the proteolytic balance in mucosal intestinal immunity

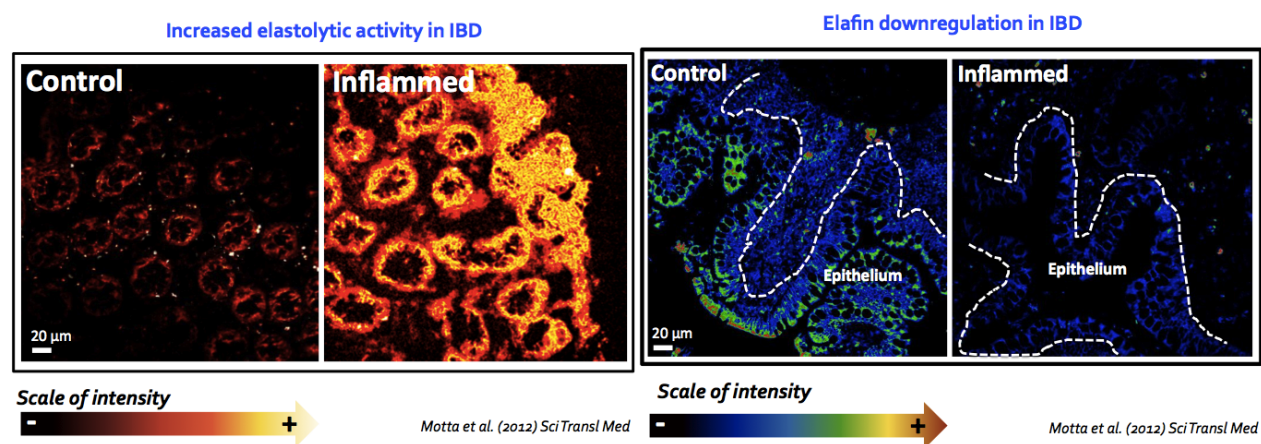
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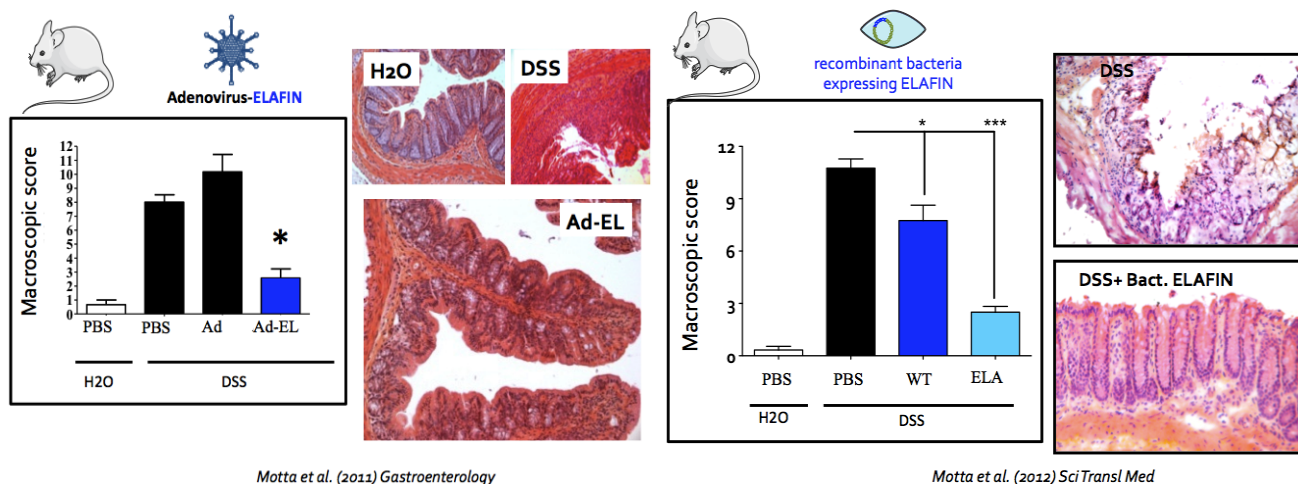
Treatment of Inflammatory Bowel Disease (IBD) represents a major medical challenge. Inflammatory processes in the gut are induced by several cells and mediators. Among them, serine proteases are mediators involved in many pathways leading to inflammation in the gut. During this thesis, we have shown that elastolytic proteases and their inhibitor were dysregulated during IBD. On one hand, colonic biopsies from IBD patients released higher amount of proteolytic activity than healthy controls did. On the other hand, the expression of elafin mRNA was downregulated in the mucosa of patients suffering from IBD. **We have hypothesized that gut inflammation could be reduced by re-equilibrating that balance in the gut, using elafin inhibitor.**

Figure 1. Elastolytic balance dysregulation during Inflammatory Bowel Disease



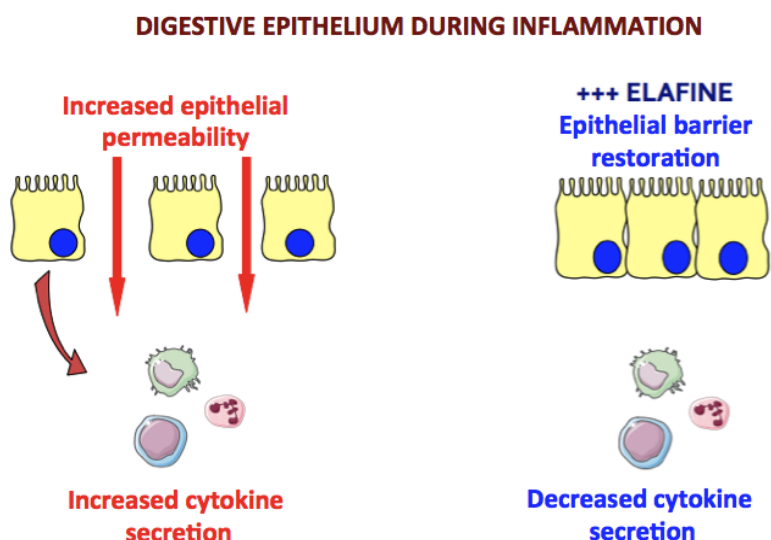
We have developed several in vivo approaches to evaluate the therapeutic properties of elafin. We have used recombinant viral vectors and recombinant lactic acid bacteria to express transiently elafin in the gut during colitis.

**Figure 2. Elafin administration reduce severity of colitis in mice models**



We have also evaluated in vitro the role of elafin in the physiology of human intestinal epithelial cells.

**Figure 4. Elafin : guardian of digestive epithelium homeostasis**



Using those different approaches, we have demonstrated that elafin reduced the clinical score of colitis in different models in mice, reduced the release of pro-inflammatory cytokines, reduced immune cell infiltration and also restored epithelium homeostasis during inflammation.

Long term objective of those results is to develop new therapeutical approach for humans. Elafin based treatment and particularly genetically modified bacteria producing elafin, could be used for patients suffering from IBD. This therapeutical approach may have the advantages to diminish the cost and side effects of actual treatments.

Publications:

**Motta, J. P., L. Magne, D. Descamps, C. Rolland, C. Squarzone-Dale, P. Rousset, L. Martin, N. Cenac, V. Balloy, M. Huerre, L. F. Frohlich, D. Jenne, J. Wartelle, A. Belaouaj, E. Mas, J. P. Vinel, L. Alric, M. Chignard, N. Vergnolle and J. M. Sallenave** (2011). "Modifying the protease, antiprotease pattern by elafin overexpression protects mice from colitis." *Gastroenterology* 140(4): 1272-1282.

**Motta, J. P., L. G. Bermudez-Humaran, C. Deraison, L. Martin, C. Rolland, P. Rousset, J. Boue, G. Dietrich, K. Chapman, P. Kharrat, J. P. Vinel, L. Alric, E. Mas, J. M. Sallenave, P. Langella and N. Vergnolle** (2012). "Food-grade bacteria expressing elafin protect against inflammation and restore colon homeostasis." *Science translational medicine* 4(158): 158ra144.