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Intestinal stem cell differentiation after massive small bowel resection is regulated by Notch signaling in a rat model

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Objective: Notch signaling promotes differentiation to the absorptive cell lineage rather than to the secretory cell lineage. The objective of this study was to determine the role of Notch signaling in intestinal stem cell differentiation in a rat model of short bowel syndrome (SBS).

Methods: Male Sprague-Dawley rats were randomly assigned to one of two experimental groups of 8 rats each: Sham rats underwent bowel transection and re-anastomosis, SBS- rats underwent 75% mall bowel resection. Rats were sacrificed on day 14. Illumina's Digital Gene Expression (DGE) analysis as used to determine Notch signaling gene expression profiling. Notch-related gene and protein expression were determined using Real Time PCR, Western blotting and immunohistochemistry.

Results: From 7 investigated Notch-related (by DGE analysis) genes 6 genes were up-regulated in SBS vs control animals with a relative change in gene expression level of 20% or more. A significant up-regulation of Notch signaling related genes in resected animals was accompanied by a significant increase in Notch-1 protein levels (Western Blot) and a significant increase in NOTCH-1 and Hes -1 (target gene) positive cells (immunohistochemistry) compared to sham animals. Evaluation of cell differentiation has shown a strong increase in total number of absorptive cells (unchanged secretory cells) compared to control rats.

Conclusions: Two weeks after bowel resection in rats, stimulated Notch signaling directs crypt cells population toward absorptive progenitors.

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