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To cite this article: Philippe Depeille & Jeroen P Roose (2015) Flavors of EGFR-Ras signals impacting intestinal homeostasis, Cell Cycle, 14:20, 3205-3206, DOI: [10.1080/15384101.2015.1084203](https://doi.org/10.1080/15384101.2015.1084203)

To link to this article: <http://dx.doi.org/10.1080/15384101.2015.1084203>



Accepted author version posted online: 20 Aug 2015.



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Flavors of EGFR-Ras signals impacting intestinal homeostasis

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The intestine is a highly dynamic organ with continuous renewal of the epithelial cell layer. The small intestine can be subdivided into the duodenum, the jejunum, and the ileum where villi and crypts are found (Fig. 1) whereas only crypts are present in colon. In the crypts self-renewal of stem cells and production of progeny occurs under the influence of Wnt signaling.¹ Progenitor cells enter the transit-amplifying (T/A) zone where they undergo robust expansion to produce the cell numbers to cover the epithelial surface. At the same time progenitor cells differentiate into multiple different lineages such as absorptive enterocytes, enteroendocrine cells, and goblet cells. Cells migrate up the villus toward the lumen and undergo apoptosis at the tip of the villus, completing the epithelial renewal cycle (Fig. 1). It is poorly understood how progenitor cells balance proliferation and differentiation. Wnt signaling and self-renewal of stem cells in the bottom of the crypt have been extensively studied.¹ Epidermal growth factor receptor (EGFR) signals are thought to be relevant in this dynamic T/A zone and several reports have implied that the EGFR pathway is required for intestinal development and contributes to stem cell maintenance. Mechanistically, it is not understood how the EGFR and its downstream Ras-kinase signals impact intestinal homeostasis.

Ras is a molecular switch activated through GTP-loading by Ras guanine nucleotide exchange factors (RasGEFs) in response to receptor signals, such as the EGFR. The amplitude and duration of

EGFR signaling to Ras and its downstream target MAPK (MAP kinase) affects cell fate; EGF stimulation of rat adrenal pheochromocytoma (PC-12) cells leads to transient Ras activation and proliferation. By contrast, NGF or EGF stimulation of PC12 cells overexpressing the EGFR results in sustained Ras-MAPK activation, exit from mitosis, and differentiation.² Do

EGFR-Ras signaling patterns regulate intestinal cell fate decisions? Genetic inactivation of the EGFR inhibits the cell size and proliferation of intestinal stem cells in *Drosophila*.³ Deletion of *Lrig1*, a negative regulator of EGFR signaling, leads to loss of normal intestinal stem cell homeostasis suggesting that strength or duration of signaling influence the stem cell population.⁴

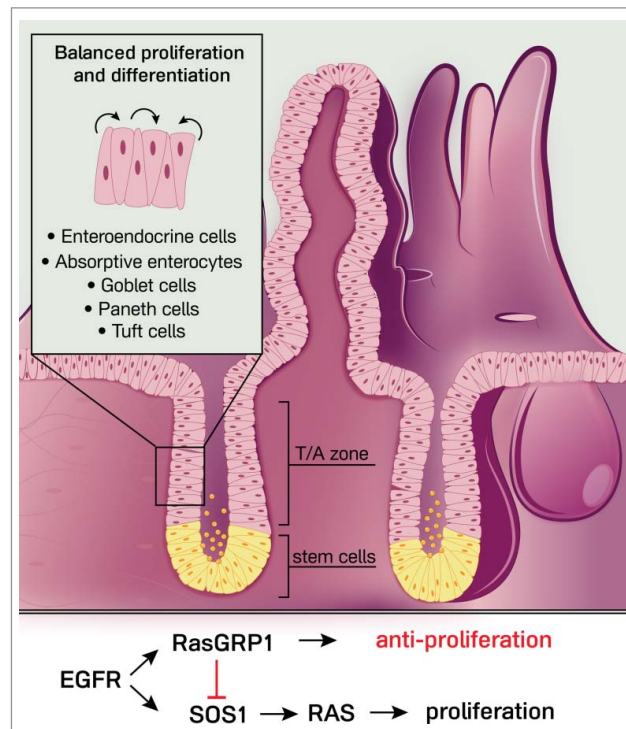


Figure 1. Continuous renewal of the epithelial cell layer in the intestine requires the production of daughter cells by stem cells. These daughter or progenitor cells expand in the T/A zone but at the same time must somehow balance such proliferation with differentiation into the various specialized cell lineages (see inset). Our recent work,⁶ uncovered that there are 2 types of EGFR signals that impact this balance. Illustration by Anna Hupalowska.

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Submitted: 08/03/2015; Accepted: 08/07/2015

<http://dx.doi.org/10.1080/15384101.2015.1084203>

Comment on: Depeille P, et al. RasGRP1 opposes proliferative EGFR-SOS1-Ras signals and restricts intestinal epithelial cell growth. *Nat Cell Biol* 2015; 17(6):804-15; PMID: 26005835; <http://dx.doi.org/10.1038/ncb3175>

We demonstrated that the type of RasGEF dictates Ras-MAPK activation patterns in lymphoid cells; RasGRP1 (Ras guanine nucleotide releasing protein-1) transmits analog Ras signals while SOS1 (Son of Sevenless-1) transmits digital Ras signals.⁵ The above-mentioned studies inspired us to investigate the role of RasGRP1 and SOS1 in intestinal epithelial cells.

In our recent publication,⁶ we have shown that these 2 distinct RasGEFs, RasGRP1 and SOS1, lie downstream of the EGFR but act in functional opposition to one another in colorectal cancer. Biochemically, RasGRP1 creates a negative feedback loop that limits EGFR-SOS1-Ras signals (Fig. 1) resulting in a dampening of the growth signal. In the context of normal intestinal homeostasis, we found that *Rasgrp1* is expressed in the crypt area and impacts homeostasis of the epithelium.⁶ Deletion of *Rasgrp1* results in an increased proliferation of epithelial cells. Produced epithelial progeny move

up quicker along the crypt-villi axis and demonstrate a higher apoptosis rate at the tip of the villi. Deletion of *Rasgrp1* increases in the numbers of goblet cells suggesting that stronger EGFR-Ras signals favor cell decisions toward the goblet cell lineage. Finally, in context of an intestinal injury model, *Rasgrp1* knockout mice showed partial protection from DSS (dextran sulfate sodium)-induced colitis and retained a relatively normal architecture of the colonic epithelium with lower grade inflammation. Previous work revealed that the EGFR positively contributes to repair of the intestine after injury in *Drosophila*,³ suggesting that protective EGFR signals may also play a role in human inflammatory bowel disease. Of note, the partial protection from DSS insult in *Rasgrp1* knockout mice may be the result from the increased epithelial turnover, from increasing mucus secretion by the higher numbers of goblet cells, or both.

Our study is the first to describe a role for the RasGEF RasGRP1 in intestinal homeostasis and responses to intestinal injury. Originally dubbed as a lymphoid-specific RasGEF with a unique role in T cell development, it is becoming increasingly clear that RasGRP1 executes critical roles in other cell systems, such as lymphoid- and myeloid- leukemias, and epithelial cells and carcinoma which we discussed here.⁷ A substantial amount of work has focused on the nature of receptor ligands and distal downstream effectors of Ras such as kinases, but not much on the RasGEFs that directly control Ras activation. Our recent work⁶ clearly shows that RasGRP1 and SOS1 are not merely redundant RasGEFs in intestinal epithelial cells. The possibility that RasGRP1 and SOS1 operate downstream of the same EGFR but may play opposing roles in the same progenitor cell in the T/A zone is a novel and intriguing concept that requires future research.

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