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Enteroendocrine Cells, A Potential Way to Control Intestinal Stem Cell Proliferation

Rihab Loudhaief and Armel Gallet*

Institut Sophia Agrobiotech, France

***Corresponding author:** *Armel Gallet, Institut Sophia Agrobiotech, UMR INRA 1355/CNRS 7254/UNS, 400 route des Chappes, BP 167, 06903 Sophia Antipolis Cedex, France, Fax: 33 (0)4 92 38 65 87, E-mail: gallet@unice.fr*

Perspective

Organisms are subjected during their lifespan to many environmental stresses such as starvation, temperature variations, chemicals, pathogens, injuries… In order to overcome the incoming stress and to yield an adapted answer, organisms have developed throughout evolution robust and conserved mechanisms such as immune response and tissue regeneration helping at maintaining their physiological equilibrium, i.e. their homeostasis. However, the maintenance of the homeostasis can be compromised in certain cases. For example, aging is characterized by an overall decline in tissue homeostasis maintenance with reduced immune function and tissue regeneration capacities and with increased baseline inflammation [1]. Homeostasis can also be disrupted upon chronic or prolonged exposure to toxic or pathogens that can cause damages to organs and tissues [2]. Another example where the homeostasis can be broken down is the predisposition of individuals harboring "silent" mutations to develop pathologies. Under stress conditions, an apparent healthy individual can indeed develop inflammatory diseases, autoimmune syndrome or cancers [3].

The digestive tract is an organ in direct contact with the external milieu facing many xenobiotics or pathogens swallowed along with the food that can harm the mucosa. In the intestine, the replacement of damaged cells relies on intestinal stem cells (ISCs) that divide to give birth to progenitor cells that subsequently differentiate to replenish the gut lining. While under normal condition the intestine is completely renewed in more or less than 2 weeks whether in mouse [4-6] or in *Drosophila melanogaster* [7,8], upon damages ISC division is accelerated (there is a switch from routine division to proliferation) and the gut is renewed in a couple of days [2]. Many signaling pathways involved in the control of ISC division/proliferation have been identified since the last decade [9,10]). Most of these signals are locally produced (referred to the stem cell niche), coming from neighboring cells such as Paneth cells or surrounding tissues such as the underlying mesenchyme/visceral mesoderm [9-12]. The production of these signals is modulated according to the (local or systemic) need at any given time, allowing the adaptation of ISC division/proliferation to environmental cues [2,13]. This process must be tightly regulated otherwise an uncontrolled ISC proliferation results in overgrowth that can lead to tumor occurrence in the case where ISCs bear a pro-oncogenic mutation.

The enteroendocrine cells (EECs) are secreting cells scattered and interspaced between enterocytes in the gut lining. EECs have long been known to make the link between the nutrient content of the gut and the brain by secreting enteroendocrine peptides that regulate digestive functions and nutritional behavior [14]. More recently, EECs have also been implicated in the local immune response by producing cytokines and anti-microbial peptides [15-18]. EECs are not yet considered as being part of the ISC niche although these cells are indirectly implicated in the control of ISC division (Figure 1A). Indeed it was previously demonstrated that EECs may influence ISC proliferation by secreting peptides regulating the production of growth factors by the niche. In *Drosophila* it has been shown that the enteroendocrine peptide Tachykinin (ortholog to TAC in mammals) locally secreted by EECs induced the production of Dilp3 (a *Drosophila* Insulin-like Growth Factors) by the visceral mesoderm [19]. Then Dilp3 promotes ISC proliferation to adapt the growth of the gut to the nutrient availability (Figure 1A) [10]. Still in *Drosophila*, Scopelliti and colleagues [20] have shown that the enteroendocrine hormone Bursicon produced by EECs is able to constrain ISC division by repressing, in the visceral mesoderm, the expression of the EGF growth factor Vein (Figure 1A). Noteworthy, the Bursicon receptor DLGR2 is the mammalian ortholog of LGR4-6. In mammals, the Glucagon like peptide-2 (GLP-2) secreted by the EECs acts on underlying myofibroblasts to induce the secretion of EGFR/ErbB ligands that further bind receptors in ISCs to stimulate their proliferation (Figure 1A) [21-23]. These data highlight that EECs can act as local regulators of ISC division/proliferation through modulation of the stem cell niche activity in both *Drosophila* and mice.

In a recent beautiful transcriptomic analysis *in vivo* in *Drosophila melanogaster*, Dutta and Colleagues identified 453 genes that were differentially expressed in EECs upon ingestion of the strong pathogen *Pseudomonas entomophila* [16]. Among these 453 genes not all are involved in the regulation of the digestive functions, the immune response or paracrine control of the expression of growth factors by the visceral mesoderm. Indeed after our own reading of the data they have released on line (http://flygutseq.buchonlab.com/resources), we found that several genes encoding for secreted factors directly implicated in the control of the ISC proliferation are modulated. In this list of genes, we noticed two Insulin-like Growth Factors (Dilp2 and Dilp3) known to control cell proliferation in many tissues in mammals [24]. In *Drosophila*, both were already known to control ISC proliferation according to the nutrient availability.

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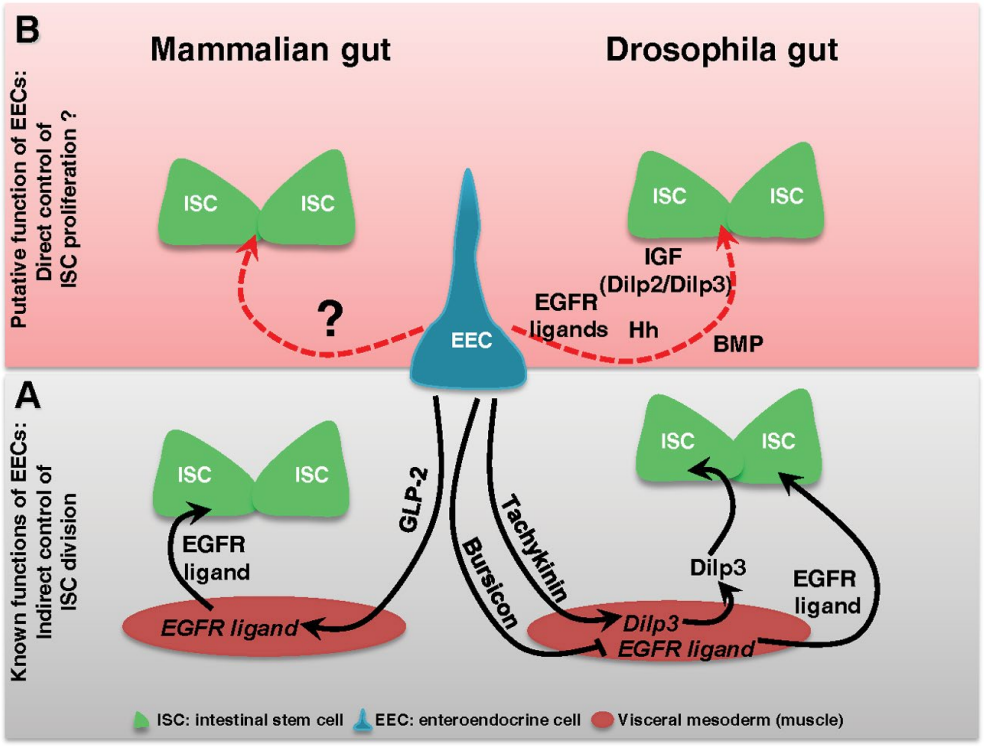

Figure 1: Enteroendocrine cells and regulation of intestinal stem cell division.

(A) Scheme summarizing the known functions of EECs in the control of ISC division in mammalian and *Drosophila* guts. The control is indirect and is mediated by the Glucagon-like peptide-2 (GLP-2) in mammals and by the enteroendocrine hormones Tachykinin and Bursicon in *Drosophila;* (B) Scheme underlying the putative more direct role of EECs in the control of ISC proliferation upon damages.

Dilp2 is normally released by the central nervous system into the circulation while Dilp3 is locally produced by the visceral mesoderm [10]. We also noticed an increased expression of two EGFR ligands (Keren and Spitz), two IL-6 cytokines orthologs (Upd2 and Upd3), the conserved growth factor Hedgehog (Hh), and two BMP ligands (Dpp and Gbb) (Figure 1B). Whereas EGFR, IL-6/JAK/STAT and Hh signaling pathways positively control ISC division, BMP signaling has a versatile function by either activating or inhibiting ISC division depending of the ligands involved. All these growth factors and cytokines are provided by the niche and they bind to their respective receptors at the surface of ISCs to control their division/proliferation in both vertebrates and *Drosophila*. Their production is generally increased upon damages to accelerate gut lining regeneration [2,9,10]. Therefore, a potential production of those different factors by EECs [16] can give to these cells an additional important role to maintain gut homeostasis, this time by sending signals directly controlling the behavior of ISCs (Figure 1B). Nevertheless, it will be necessary to investigate whether the production of these factors by EECs is playing a significant role in the control of ISC division before to conclude anything. Because of the high degree of conservation between *Drosophila* and mammals with respect to the signaling pathways that control ISC division, *Drosophila* midgut is a suitable model for such an investigation. It is indeed easy to invalidate each candidate in EECs and to assess impacts on ISC division/proliferation at steady state or upon damages. Many investigations in mammals will be also necessary before to definitively unravel the roles of EECs in the control of ISC behavior.

These axes of investigations will probably help at designing cancer therapies specifically targeting EECs. In this perspective, it should be noted that because of the primary role of EECs in the digestive functions, it will be of utmost importance to investigate the relationship between the diet and production of these growth factors by the EECs. Also, identifying which types, where and how EECs control the production of growth factors regulating ISC behavior is essential because of the complexity of the intestine physiology.

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