The Physiologic Roles of the Subepithelial Platelet-derived Growth Factor Receptor α -positive Cells in the Colon

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Summary

Platelet-derived growth factors (PDGFs) exist in epithelial cells, endothelial cells and fibroblasts of animals and play roles in cell proliferation, survival and migration.¹ It is composed of 4 subtypes (A, B, C and D), and their receptors (PDGFRs) have 2 subtypes (α and β). Platelet-derived growth factor receptor α -positive cells (PDGFR α^+ cells) in the gastrointestinal tract is known as fibroblast-like cells. Recently, it is noted, the PDGFR α^+ cells in the muscle layers of the gastrointestinal tract are involved in purinergic motor neurotransduction. However, PDGFR α^+ cells are distributed at all subepithelial lesion and the physiologic role is not yet established.

Recently, Kurahashi et al² evaluated the distribution in subepithelial cells in the mouse and human colon, and the phenotype and potential role of those cells. They assessed the subepithelial PDGFR α^+ cells connected to each other and located just beneath the colonic epithelium, with its pericryptal sheaths from the base to the top of crypts being sparse at the bottom of crypts. Subepithelial α -smooth muscle actin-positive (α -SMA $^+$) cells (myofibroblasts) were adjacent to, but distinct from, subepithelial

PDGFR α^+ cells, were always located at the mesenchymal side of subepithelial PDGFR α^+ cells, and were distinct from smooth muscle myosin-positive cells. They performed the double labeling of PDGFR α with protein gene product 9.5 (PGP9.5) and α -SMA with PGP9.5. PGP9.5 immunoreactive fibers were found at the mesenchymal surface of subepithelial PDGFR α^+ cells, and some fibers were found at the epithelial side of the myofibroblasts. This data show that the promoter driving *pdgfra* expression is active in subepithelial PDGFR α^+ cells but not in subepithelial myofibroblasts. Quantitative polymerase chain reaction (qPCR) was performed on cDNAs obtained from sorted PDGFR α^+ cells and unsorted cells representing all cell types dispersed from the mucosa. These data showed that transcripts of *pdgfra* were significantly enriched in PDGFR α^+ cells, and subepithelial PDGFR α^+ cells also expressed Toll-like receptors (*Tlr4*, *Tlr5* and *Tlr9*), purine receptors (*P2ry1*, *P2ry2* and *P2ry4*), and 5-hydroxytryptamine receptors (*Htr4*) more strongly compared with the other cell types in mucosa. *Htr3a* and *Htr3b* expressions were much lower in PDGFR α^+ cells than in other mucosal cells. Other qPCR analysis data revealed that subepithelial PDGFR α^+ cells expressed hedgehog signaling molecules (*Ptch1* and *Gli1*) at much greater levels than other cell types.

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They concluded that PDGFR α is a unique immunolabel for a population of cells that might correspond to the cells identified by electron microscopy as pericryptal fibroblasts. Subepithelial PDGFR α ⁺ cells form a sheath just beneath the epithelium and cover crypts from their base to the luminal surface of epithelium. The roles of these cells in physiological and pathophysiological processes are unknown, but the labeling techniques and the use of a reporter strain that we have characterized will make comprehensive studies of these cells possible for the first time. Several key transcripts are expressed by these cells in mouse, suggesting these cells may have modulatory functions in immune and sensory responses and in the maintenance of mucosal homeostasis.

Comments

The functional roles of PDGFR α ⁺ cells was limited up to recently. It expresses the small-conductance Ca²⁺-activated K⁺ (SK) channel protein as shown by immunohistochemistry.³ Koh and Rhee⁴ dealt with the review of the ionic conductance in response to post-junctional potentials. According to this review, purines (ATP and β -nicotinamide adenine dinucleotide [β -NAD]) are coupled to Gq/11 protein and activate conductance through inositol 1,4,5-triphosphate receptor (IP₃R) in PDGFR α ⁺ cell and smooth muscle cells. However, PDGFR α ⁺ cells not only are distributed in the gastrointestinal smooth muscle, but also exist in the lamina propria, which is a complex region lying beneath the epithelial cells of the gastrointestinal tract. There have been a

few reports on the physiologic role of subepithelial PDGFR α ⁺ cells. This study reported robust expression of PDGFR α in population of subepithelial cells in the colon. The initial gene expression analysis performed yielded interesting and novel findings of several toll-like receptors, purinergic receptors, 5-hydroxytryptamine receptors, and hedgehog signaling molecules transcriptions.

In conclusion, this study showed both the distribution of PDGFR α ⁺ cells in subepithelial area and several key transcripts expressed by these cells. The authors suggested the subepithelial PDGFR α ⁺ cells occupy an important niche in the lamina propria and may function in the transduction of sensory and immune signals and in the maintenance of mucosal homeostasis.

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