5-hydroxyindoleacetic acid, a new ligand for GPR35, acts an important role in inflammatory disease

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Research Highlight

5-Hydroxyindoleacetic acid, a new ligand for GPR35, plays an important role in inflammatory disease

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G protein-coupled receptor 35 (GPR35), originally an orphan receptor, was discovered in 1998. At that time, the lack of pharmacological tools and convincingly defined endogenous ligands of GPR35 hindered the understanding of its functions and therapy [1]. De Giovanni et al. [2] recently discovered that 5-hydroxyindoleacetic acid (5-HIAA) is a new ligand of GPR35. Notably, 5-HIAA can promote neutrophil recruitment to inflammatory sites to clear pathogenic bacteria by activating GPR35.
Interestingly, this new ligand is derived from platelets and mast cells. Based on this, we briefly commented that platelet and mast cell-derived 5-HIAA activates GPR35 on neutrophils to promote the inflammatory process.

The biggest innovation in this paper is that platelet and mast cell-derived 5-HIAA is discovered as a new endogenous ligand of GPR35. De Giovanni et al. [2] demonstrated that GPR35 is activated by 5-HIAA to promote neutrophil recruitment to inflammatory lesions in a thioglycolate-induced peritonitis model and Listeria infection model. What are the main sources of 5-HIAA in the process of neutrophil recruitment? In the screening of the ligand activity of GPR35, the contents of activated platelets were found to have strong ligand activity. In platelets, abundant monoamine oxidase can catalyze the conversion of 5-hydroxytryptamine (5-HT) to 5-HIAA. Additionally, they found that a large number of platelets accumulate in inflamed endothelial tissues. Moreover, GPR35 deficiency significantly decreased the binding of platelets and neutrophils, suggesting that platelets play a crucial role in neutrophil recruitment. More importantly, 5-HIAA caused the internalization of murine and human GPR35 on the cell surface in a dose-dependent manner but not the internalization of other GPCRs. Therefore, platelet-derived 5-HIAA is the ligand of GPR35 and can be used as a chemokine of GPR35+ cells. The discovery of 5-HIAA paves the way for future research on the function of GPR35.

5-HIAA is the final metabolite of 5-HT and widely exists in humans. It has been reported that 5-HT is associated with neurological and psychiatric diseases and can be used as a potential biomarker [3]. Platelets are only the storage place of 5-HT but cannot synthesize 5-HT. 5-HT is mainly stored in dense electron opaque particles of platelets [4]. However, where does 5-HT in platelets come from? Mast cells may be a new source of 5-HT. A previous study indicated that intestinal chromaffin cells are important sites for the synthesis and storage of 5-HT. Interestingly, De Giovanni et al. [2] found that the activation of peritoneal mast cells by lipopolysaccharide could also secrete a large amount of 5-HIAA. Neutralizing 5-HIAA with a 5-HIAA antibody can inhibit GPR35-mediated neutrophil migration. All these results indicate that platelets and mast cells are the main sources of 5-HIAA. We believe that platelet-derived 5-HIAA in the lumen mainly promotes the rolling and adhesion of neutrophils with platelet clusters, while mast cell-derived 5-HIAA determines the direction of neutrophils outside the lumen. Both platelet-derived 5-HIAA and mast cell-derived 5-HIAA promote neutrophil recruitment to inflammatory sites. These pieces of
evidence indicate that the effect of neutrophils on inflammatory recruitment needs the assistance from other cells, such as platelets and mast cells.

Although some studies indicated that 5-HT can directly mediate neutrophil recruitment [5], we prefer that 5-HT and 5-HIAA work together to promote the recruitment of neutrophils. Moreover, we believe that neutrophil adhesion and migration are very important in the process of neutrophil recruitment to inflammatory sites. However, the process by which GPR35 promotes neutrophil adhesion with platelets and transdermal migration is not described in detail in De Giovanni’s study. Neutrophil adhesion and migration are mediated by endothelial cell adhesion molecules and endothelial selectin and integrin ligands [6]. How does GPR35 promote neutrophil adhesion with platelets? We suspect that GPR35 is involved in the receptor-induced neutrophil shape change and promotes the cytoskeleton remodeling of neutrophils through G12/G13-mediated or Gai-mediated Rho/Rho kinase-dependent ERM (ezrin/radixin/moesin) phosphorylation regulation [7,8]. We believe that there is a close relationship between platelet activation and neutrophil recruitment.

At present, a variety of drugs have been used in the clinic to treat mental diseases by changing the metabolic process of 5-HT, which also inevitably affects 5-HIAA. For example, fluoxetine is an inhibitor of 5-HT absorption. Researchers fed fluoxetine continuously for three weeks in mice with Listeria-inflamed skin, and found that neutrophil recruitment was significantly decreased in wild-type mice, but did not change significantly in GPR35-deficient mice. Phenelzine is an inhibitor of monoamine oxidase, which can inhibit the synthesis of 5-HIAA in platelets and mast cells. De Giovanni et al. [2] also found that phenelzine had similar effects to fluoxetine. These results indicate that inhibiting 5-HIAA has important therapeutic potential for inflammation diseases. GPR35 may be used as a target for inflammatory therapy to develop new anti-inflammatory drugs.

In addition, we believe that 5-HIAA can be regarded as a new inflammatory index that can be used as a reference standard for the diagnosis of an inflammatory disease. 5-HIAA can also provide a reference standard for the prognosis of the disease and the adjustment of late treatment plan. Moreover, GPR35 has been proven to be involved in the development of intestinal inflammation and colon cancer [9], which may open a new door for the treatment of cancer.

Of course, some limitations are found in De Giovanni’s study. For example, the
transport process of 5-HT and 5-HIAA between peripheral cells is unclear. It is well known that platelets transport 5-HT into the cell through 5-HT transporters (5-HTT) and store it in dense granules [10]. Here, we believe that there are two transport forms of 5-HT, active transport and passive transport, in platelets. When platelets are activated, 5-HT is converted into 5-HIAA and is released to promote neutrophil recruitment. In addition, platelets and mast cells release many other mediators including chemoattractants. 5-HIAA may act in the context of many other mediators. In the future, it will be necessary to explore the mechanism of neutrophil recruitment.

Therefore, the function of platelets is not limited to hemostasis and coagulation, platelets also regulate the function of neutrophils to mediate the inflammatory response [11]. In fact, neutrophils also regulate the function of platelets by releasing inflammatory factors such as granulocyte colony-stimulating factor [12]. Neutrophils can also affect platelet activation and thrombosis. This interaction promotes the activation of platelets and the recruitment and migration of neutrophils. The authors found that platelet-derived 5-HIAA can promote neutrophil recruitment, which provides a basis for this phenomenon. Of course, 5-HIAA is not the only contributor to neutrophil recruitment. Other neutrophil recruitment mechanisms should be further explored as well.

In conclusion, De Giovanni et al. [2] found that platelet- and mast cell-cell-derived 5-HIAA is a new endogenous ligand of GPR35, which plays a crucial role in neutrophil recruitment (Figure 1). They found a new mechanism of platelet involvement in inflammation and provided a new target for the treatment of inflammation. 5-HIAA may have broad prospects in future studies on platelets in inflammatory diseases.

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**Conflict of Interest**

The authors declare that they have no conflict of interest.

**References**


Figure legend

**Figure 1 5-HIAA from platelets and mast cells activates GPR35 to promote neutrophil recruitment**  
Intestine-derived and mast cell-derived 5-HT is stored in the compact body by platelets through 5-HTT. When platelets are activated, 5-HT is converted into 5-HIAA, which is released into the bloodstream and binds with neutrophil GPR35 to promote neutrophil recruitment to inflammatory sites. GPR35 may promote neutrophil cytoskeleton remodeling and migration by phosphorylating Rho/Rho kinase-dependent ERM and activating Src.
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