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Epithelial sentinel: Selective expression of CD123, the α chain of the IL-3 receptor, on distinct digestive and respiratory surfaces

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Abstract

Background and purpose: *Epithelial tissue, functioning as a protective barrier, has mechanisms to recognize an array of external disturbances and threats and to send signals to the immune system. Here we report the uncovering of the selective expression of CD123 on epithelial cells lining distinct surfaces of the digestive system and lungs.*

Materials and methods: *The expression level of CD123, the α chain of the heterodimeric receptor for Interleukin-3, was detected by immunohistochemical staining.*

Results: *We found high expression of CD123 on pancreas duct cells, intrahepatic bile ducts epithelial cells, and alveolar epithelium, but not on hepatocytes, gastric mucosa, duodenal, and colon mucosa. The CD123 expression on carcinoma specimens showed the same pattern as the tissue of origin.*

Conclusions: *We postulated that CD123 expression is characteristic of the epithelium of normally germ-free compartments that is, in steady state, quiescent, in terms of low turnover and low cytokine production. Upon infection and subsequent inflammation, IL-3 produced by activated immune cells may contribute to the restoration of the epithelial barrier by enhancing epithelial cell proliferation and cytokine production.*

INTRODUCTION

CD123 is the α chain of the heterodimeric receptor for Interleukin-3 (IL-3) that belongs to the type I cytokine receptor family. The α chain is a transmembrane glycoprotein whose extracellular domain binds IL-3 with low affinity. For high-affinity ligand binding common β (βc) subunit is necessary. The same βc chain (CD131) is shared by receptors for IL-3, GM-CSF, and IL-5, cytokines that have an essential role in hematopoiesis by inducing and controlling the proliferation and differentiation of hematopoietic pluripotent stem cells and progenitor cells *(1)*. The α chain, which is cytokine-specific, mediates ligand binding, whereas βc has a function in downstream signaling. The signals sent by the βc chain are dependent on the specificity of the α chain, i.e. cytokine engaged. The binding of these tree cytokines to their receptors triggers signal transduction through JAK/STAT, MAPK, and PI3-kinase/Akt pathways, activating transcription of genes that regulate cell cycle progression and DNA synthesis, and upregulate antiapoptotic regulatory molecules *(2)*. In that way, these cytokines promote cell survival, proliferation, differentiation, and also mature leukocyte effector functions.

Primarily, IL-3 was considered a multi-CSF because of its function in myelopoiesis *(3)*. Later on, it was found that the IL-3 receptor is expressed not only on granulocyte-monocyte and dendritic cell progenitors but also on mature cells, having a role in basophils and mast cells degranulation and activation of plasmacytoid dendritic cells *(4)*. Currently, multiple functions of this pleiotropic cytokine are highlighted. High-affinity receptors for IL-3 are expressed in various tissues influencing many biological systems. Except on myeloid, the IL-3 receptor was found on lymphoid cells, vascular endothelial cells, and in many organs.

The bone marrow stromal cells produce IL-3 at very low levels. IL-3 is produced mainly by activated T lymphocytes, monocytes/macrophages, and mast cells, suggesting its role not only in hematopoiesis but in the regulation of immune response as well. IL-3 activates T and B lymphocytes and various subgroups of innate immune cells and regulates their migration by altering the expression of adhesion molecules on vascular endothelial cells. It was postulated that IL-3 acts as a proinflammatory cytokine, transmitting signals that promote proliferation, differentiation, and effector functions of target cells *(5-8)*, bridging innate and adaptive immunity. Also, IL-3 provides signals for silencing proinflammatory response, protecting tissues from injury.

In addition, the α chain of the IL-3 receptor is overexpressed in some hematological malignancies and contributes to the growth of leukemic cells *(9)*. Although data about the expression of IL-3 receptors in the solid tumor are limited, some studies revealed enhanced proliferation of tumors after IL-3 treatment *(10)*. Here we describe the expression of CD123, the α chain of the IL-3 receptor, on the epithelium of healthy and tumorous tissue specimens of the digestive system and lungs. The expression level of CD123 was detected by immunohistochemical staining (IHC). To our knowledge, this is the first report about distinct CD123 expression on epithelial cells of different organs.

MATERIALS AND METHODS

Immunohistochemistry

Paraffin-embedded tissue samples were obtained from the Department of Pathology, University Clinical Center Kragujevac, Kragujevac, Serbia. The study was approved by the local Ethical Committee (01/22/92) and prior to initiation written informed consent was obtained from all subjects according to the Declaration of Helsinki.

Paraffin-embedded tissue blocks were consecutively cut to a thickness of 4–5 µm. Each section was deparaffinized and rehydrated with graded ethanol. Antigen retrieval was performed by microwave heating for 20 minutes in 10 mM sodium citrate buffer (pH 6.0). The activity of endogenous peroxidase was blocked with a 3% hydrogen peroxide solution for 10 min at room temperature. After washing with PBS, slides were incubated with mouse CD123 monoclonal antibody (NCL-L-CD123, Leica Biosystems Newcastle, UK at a 1:100 dilution) for 60 min in a humid chamber. Sections were washed in PBS three times and then incubated with secondary antibody (EnVision FLEX, High pH (Link), HRP. Rabbit/Mouse, Agilent Technologies, Inc., USA) for 15 min at room temperature. The bound antibodies were visualized by 10 minutes incubation with DAB Flex chromogen, and all the slides were counterstained with hematoxylin. Negative controls were treated in the same way with the primary antibodies omitted. Positive controls consisted of tissue known to contain the protein of interest. An Olympus microscope (BX50 model) equipped with a digital camera was used to prepare x200.

To inspect and confirm our results, a second staining run was performed with the same paraffin-embedded tissue samples using primary rabbit CD123 polyclonal antibody (PA5-119920 Invitrogen, Thermo Fisher Scientific UK, at a 1:200 dilution) and secondary anti-rabbit antibody (Epredia™ UltraVision™ Quanto Detection System HRP, Thermo Scientific, USA).

All tissue specimens were investigated independently by two pathologists. The samples were analyzed using a semiquantitative modified scoring system, according to the percentage of normal, tumor, and metastatic tissue stained with CD123 and intensity of staining. The staining intensity was scored as 0 for negative (no immunoreactivity), 1 for low intensity, and 2 for high intensity of CD123 expression.

RESULTS

Pancreas duct cells display high expression of CD123

Immunohistochemical analysis of normal pancreatic tissue revealed that all epithelial cells of intercalating pancreatic ducts and major pancreatic duct show very high expression of CD123. A proportion of pancreatic acinus cells were weakly stained for CD123 (Figures 1A and 1B). In pancreatic adenocarcinoma cells a high level of CD123 was detected on most of the cells (Figure 1C). A representative section of pancreatic ductal adenocarcinoma with liver metastasis illustrates potent CD123 staining of cancer cells but lack of staining in normal hepatocytes (Figure 1D). The results of the IHC analysis of normal and neoplastic pancreas specimens showed that normal pancreas duct cells, primary and metastatic pancreatic ductal adenocarcinoma cells, express a high level of CD123.

CD123 is highly expressed on intrahepatic bile ducts epithelial cells

The CD123 expression was also examined on normal liver tissue. Strong positive staining was localized on intrahepatic bile ducts epithelial cells, but hepatocytes were

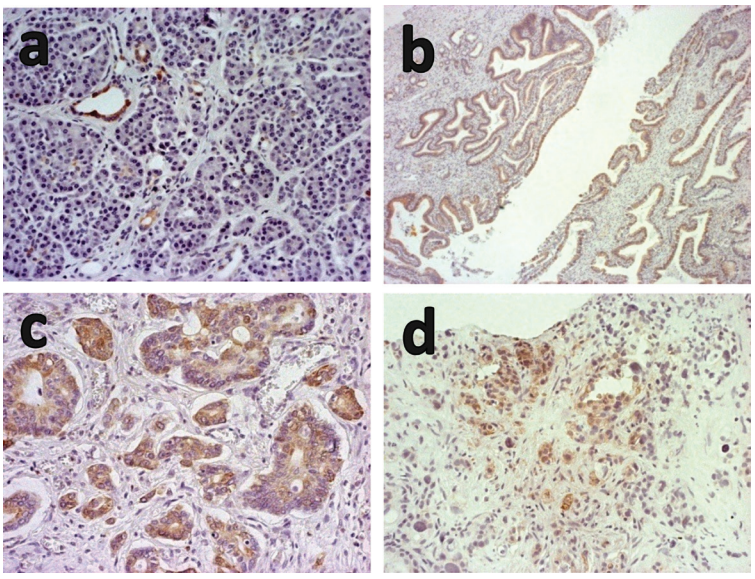

Figure 1. *Immunohistochemistry in representative normal and neoplastic pancreas specimens. (**A**) Normal pancreas, intercalating pancreatic ducts. (**B**) Normal pancreas, major pancreatic duct. (**C**) Primary pancreatic ductal adenocarcinoma. (**D**) Pancreatic ductal adenocarcinoma with liver metastasis. Original magnification x200.*

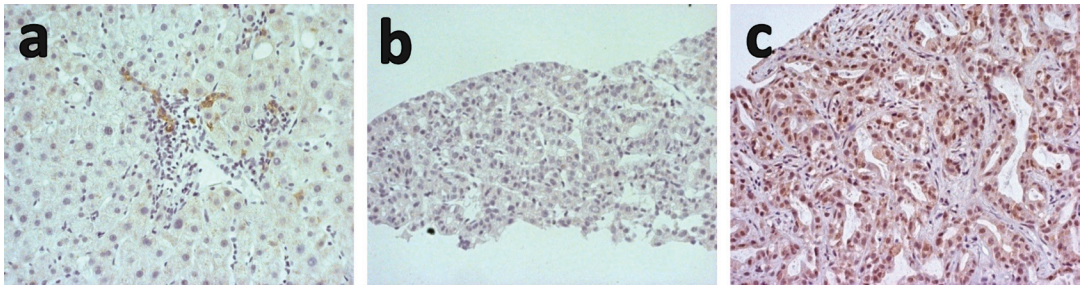

Figure 2. *Immunohistochemistry in representative normal and neoplastic liver specimens. (**A**) Liver bile ducts epithelium. (**B**) Hepatocellular carcinoma. (**C**) Cholangiocarcinoma. Original magnification x200.*

negative for CD123 staining (Figure 2A). CD123 expression was also investigated in tissues from human hepatocellular carcinoma and cholangiocarcinoma. A complete lack of staining was found in hepatocellular carcinoma cells (Figure 2B), while the cholangiocarcinoma specimens demonstrated strong CD123 staining (Figure 2C).

Gastric epithelium is negative for CD123 staining

The expression of the CD123 biomarker was further investigated on the normal epithelium of gastric mucosa and gastric cancer tissue. Normal gastric mucosa, gland epithelium, and gastric cancer tissue showed no immunoreactivity on CD123 antibodies (Figures 3A and 3B).

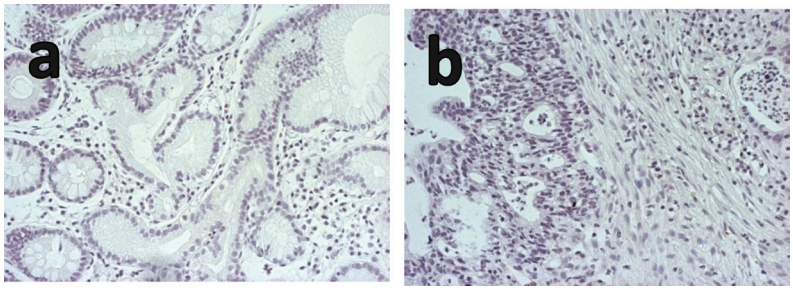

Figure 3. *Immunohistochemistry in representative normal and neoplastic gastric specimens. (**A**) Normal gastric mucosa. (**B**) Primary gastric adenocarcinoma. Original magnification x200.*

Duodenal and colon mucosa are negative for CD123 staining

We further investigated the expression level of CD123 on the normal epithelium of duodenal mucosa, as well as crypt epithelium and Brunner's glands, and concluded that all cells of duodenal mucosa and Brunner's illustrate lack of staining (Figure 4A). In this way, we also analyzed the expression of CD123 on normal colon mucosa, colon adenocarcinoma, and lung metastasis of colon cancer. We found that all cells of normal colon epithelium were negative for CD123 staining (Figure 4B). Similarly, CD123 expression was not detected on colon adenocarcinoma cells and tumor cells of lung metastasis of colon cancer (Figure 4C).

CD123 is strongly expressed on the alveolar epithelium

Although cells of lung metastasis of colon cancer were negative for CD123, strong immunopositivity was observed in the normal alveolar epithelium (Figure 5A). In order to validate this finding and to subsequently assess the expression of this biomarker in lung epithelium, we performed immunostaining of primary lung adenocarcinoma. Our results demonstrated high CD123 expression on lung adenocarcinoma cells (Figure 5B).

To verify our results, the consecutive tissue sections from the same paraffin-embedded tissue samples were stained with rabbit CD123 polyclonal antibody (as described in MATERIALS AND METHODS). Labeling with antibodies raised in a different species showed the same pattern and the level of CD123 expression and confirmed our findings (data not shown).

DISCUSSION

The epithelium is a continuous layer of cells that covers all external surfaces of the body and internal superficies of body cavities, duct structures, glands, and blood vessels. The epithelium has a variety of functions, including absorption, secretion, sensory reception, but the main one is the protection of underlying tissues against the environment. The barrier integrity is maintained by highly regulated cellular turnover, i.e., replacement of damaged or dead cells with new, differentiated epithelial cells *(11)*. This process occurs by different dynamics in distinct epithelial structures. Epithelial tissue lining the intestine, which is continuously exposed to physical, chemical, and biological insults, has a rapid cell turnover of 4-5 days. The gastric epithelium damage and repair are constant and normal physiological events *(12)*. On the other hand, some other tissues, like the lung and pancreatic epithelium, have a very low level of cellular turnover *(13)*. However, even those tissues have exceptional regenerative potential. Stress (e.g. malnutrition) or damage (infection, irradiation) speed up the turnover rate.

Epithelium has an important role in the immune defense against pathogens, not only as a physical barrier but also as a sensor of danger and participant in the immune response. Epithelial cells are recognizing microorganisms

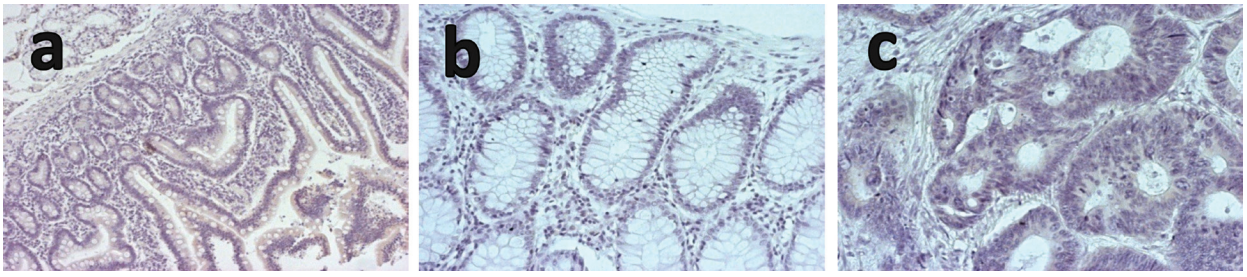

Figure 4. *Immunohistochemistry in representative normal duodenum, normal and neoplastic colon specimens. (**A**) Normal epithelium of the duodenum. (**B**) Normal colon epithelium. (**C**) Colon adenocarcinoma. Original magnification x200.*

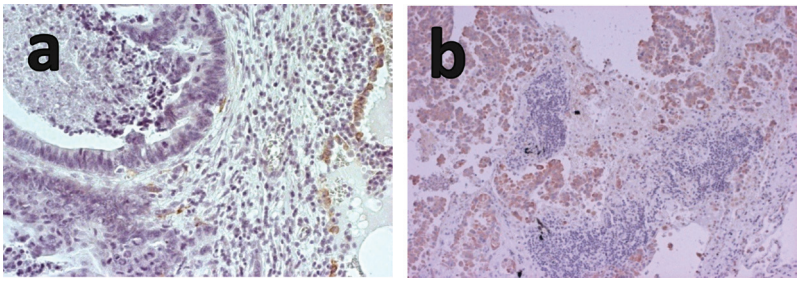

Figure 5. *Immunohistochemistry in representative lung specimens. (**A**) Lung metastasis of colon cancer. (**B**) Primary lung adenocarcinoma specimens. Original magnification x200.*

by pathogen-recognition receptors (PRRs) and in response produce and secrete diverse molecules (enzymes, antimicrobial peptides, ROS, etc.) that neutralize or kill pathogens *(14)*. In addition, epithelial cells produce cytokines that participate in the initialization and regulation of both innate and adaptive immune responses. On the other side, epithelial tissue-resident macrophages, mast cells, dendritic cells, and intraepithelial lymphocytes also secrete cytokines that modify the epithelial cytokine response. Mutual communication between these cells and epithelial cells through cytokine network is of the outmost importance for efficient defense against pathogens *(15)*.

The epithelium of the gastrointestinal tract is constantly challenged by different microbes, and complex mechanisms exist to provide appropriate reactions to the presence of commensal and pathogenic microorganisms. However, there are areas in the body that are normally free of microorganisms. The epithelium lining initially sterile compartments has to be able to recognize infection and respond adequately. In the first place, the epithelial layer damaged by microorganisms and inflammation has to be repaired, i.e., cellular turnover has to be accelerated. Sun *et al. (16)* have shown increased epithelial turnover in normally low-turnover organs (kidney, liver, salivary gland, and pancreas) in mice infected with murine cytomegalovirus. Urothelium, which has a very low basal level of renewal (up to 40 weeks), can be regenerated within one week in response to uropathogenic *E. coly (17)*. Mechanisms that direct cellular turnover are complex and still not completely elucidated. It is reasonable to assume that tissues with low turnover express some molecules other than those with a high turnover rate, which would favor faster regeneration.

In our study, we investigated the expression of CD123, the α chain of the IL-3 receptor, on different tissue specimens. Here we demonstrated that CD123 expression is characteristic of epithelium that is, in steady state, quiescent, in terms of low turnover and low cytokine production. Alveolar epithelium and epithelium of pancreas ducts and intrahepatic bile ducts, which are normally out of reach of microorganisms, showed high CD123 expression. Contrarily, hepatocytes, gastric, duodenal, and colon mucosa were negative for CD123. IL-3, in the first place, promotes survival and proliferation. When epithelium of normally germ-free compartments recognize microorganisms by PRRs, cells send signals to epithelial tissue-resident innate immunity cells. Those cells activate and start to produce cytokines. In ongoing inflammation, both microorganisms and the immune response entail damage to epithelial cells. IL-3 produced by activated mast cells, monocytes/macrophages, and activated T lymphocytes may contribute to the restoration of the epithelial barrier by enhancing the proliferation of epithelial cells. Furthermore, in inflammatory conditions, cytokines produced by cells of innate and adaptive immunity augment cytokine production in epithelial cells. Therefore, as IL-3 promotes the effector functions of activated immune cells, it may have a role in enhancing epithelial cell cytokine production.

The CD123 expression on carcinoma specimens showed the same pattern as the tissue of origin. Ductal adenocarcinoma, cholangiocarcinoma, and lung adenocarcinoma showed high CD123 expression, while hepatocellular carcinoma, gastric, duodenal, and colon adenocarcinoma cells were negative for CD123. Given the role of IL-3 in survival and proliferation, the expression of its receptor may be advantageous for cancer cells.

IL-3 and its receptor are for a long time investigated as therapeutic targets for some types of cancer. In hematological malignancies characterized by high CD123 expression on malignant cells, different strategies of inhibition of IL-3 binding and signaling are tested in ongoing clinical trials *(18, 19)*. The attempts of IL-3 application after chemotherapy of non-hematologic malignancies to induce regeneration of granulocytes and platelets were disappointing since no significant benefit was confirmed in clinical studies *(20, 21)*. However, in those trials involving patients with solid tumors, more attention has been paid to the effect of IL-3 on hematological parameters and less to the effect on the tumor itself; therefore, the data relating to IL-3 impact on tumor growth *in vivo* are poorly available. Numerous *in vitro* studies have investigated the effect of IL-3 on tumor cell lines. The data are contradictory, since some researchers showed that IL-3 can promote the growth of cancer cells, whereas other authors indicated that it may exert anticancer activities. Namely, *in vitro* studies showed that IL-3 can stimulate the growth of some, but not all, nonhematopoietic malignant cell lines derived from different histological cell types *(22–25)*, and Izquierdo *et al.* showed that in tumor cells taken directly from patients with various solid tumors, IL-3 exerts either no effect or, in a smaller number of samples, the growth stimulation or inhibition, depending on the histological origin of the tissue *(26)*. These data are in agreement with our findings of distinct CD123 expression on epithelial cells of certain organs and on cancer cells originating from those tissues.

We acknowledge that this study has certain limitations. First, the relatively small sample size reflects the exploratory nature of our work, and larger cohorts will be necessary to validate these findings. Second, while functional experiments were not performed, our results provide a basis for future studies.

CONCLUSION

The attempts of IL-3 application in cancer patients should be taken with caution. The results of our study can be useful in searching for new treatment options.

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