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Chemokine decoy receptor D6 in inflammatory bowel disease (IBD) and IBD-associated colon cancer

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Thirteen years ago the first decoy receptor was identified (ie, IL-1 receptor type II). Lacking a cytoplasmic domain, it binds IL-1β, without triggering signal transduction. Thus the receptor was defined as “structurally incapable of transducing signal but able to recognise the agonist with high affinity and specificity”1 acting as a “sink” to prevent ligand activity. Since then, other cytokines and chemokines (mostly pro-inflammatory) have been found to be similarly regulated.2 Their mechanism of action is to compete with functional receptors for ligand binding and in some instances target the complex for degradation. Several decoy receptors for the chemokine family have been identified (eg, D6, DARC and CCXCKR). Common to all are mutations in or around the DRY motif that prevent G protein coupling and intracellular signal transduction.

D6 was first cloned in 19973 and its designation is that of the clone from Colorado, USA. Lacking a cytoplasmic domain, it binds IL-18 without triggering signal transduction. Several decoy receptors for ligand binding and in some cases target the complex for degradation. Several decoy receptors for the chemokine family have been identified (eg, D6, DARC and CCXCKR). Common to all are mutations in or around the DRY motif that prevent G protein coupling and intracellular signal transduction.

D6 is expressed by lymphatic endothelial cells (LEC) at sites of primary antigen exposure, such as the gut, skin, lung and placenta. In health, D6 is mostly found in intracellular vesicles, from where it rapidly cycles to the cell membrane upon exposure to inflammatory CC chemokines.4 D6 expression has been thought to be restricted to afferent LEC. But its function as a chemokine scavenger at this site location is not obvious, as chemokines appear sufficiently separated by intervening tissue to be scavenged by LEC D6 (hypothesis A) (figure 1). Recently, expression of D6 has been demonstrated on leukocytes, predominantly on B cells and dendritic cells within inflamed tissues. By contrast, these will be critically positioned to act as scavengers (hypothesis B). This concept is now being challenged by the work of Vetrano et al6 (see page 197).

**RELATIVE ROLE OF LEUKOCYTE AND LYMPHATIC D6**

Vetrano observed that D6 expression is increased in leukocytes and colonic lymphatic vascular beds from inflammatory bowel disease (IBD) and IBD-associated cancer.7 D6 also plays a role in dextran sulfate sodium (DSS) colitis, as there is greater inflammation and accumulation of CC chemokines during DSS colitis in D6-deficient mice, associated with increased leukocytic infiltration and weight loss. This is in keeping with prior studies in which D6-deficient mice have been shown to be more susceptible to inflammatory-mediated tissue damage.7 8 Most importantly, they show that selective D6 deficiency on haematopoietic cells had no impact on DSS colitis, while restoration of D6 to the haematopoietic compartment failed to rescue the exacerbation of colitis caused by D6 deficiency. These findings suggest that in the context of acute intestinal inflammation, expression of LEC D6 and not haematopoietic D6 is critical to modulate colitis.

Impaired resolution of inflammation likely contributes to chronic injury and progression to malignancy. In fact, there is a robust link between chronic inflammation and cancer. Along the gastrointestinal tract, there is increased risk of oesophageal adenocarcinoma associated with chronic acid reflux, gastric cancer with *Helicobacter pylori* infection, cholangiocarcinoma with primary sclerosing cholangitis, hepatoma with viral hepatitis, lymphoma with coeliac disease and colon cancer with IBD. A role for leukocyte-derived chemokines in tumour initiation and progression has been postulated. The composition of leukocyte infiltrates in solid tumours is directly related to the localized production of chemokines, matrix metalloproteinases and angiogenic factors which contribute to tumour progression. C-C chemokines CCL2, CCL4 and CCL5 directly induce MMPS production from macrophages and all directly correlate with tumour progression in human breast and squamous-cell carcinomas.9 Whether chemokine scavenging by D6 may play a role in these processes is unknown. The data by Vetrano and colleagues supports an affirmative answer. D6-deficient mice displayed increased susceptibility to azoxymethane-induced colitis-associated colon cancer, a greater number of active lesions,
accelerated epithelial cell turnover and altered expression of junctional proteins. Furthermore, the exacerbated disease severity in D6-deficient mice correlated with increased colonic leukocyte infiltration, supporting a link between leukocyte-derived chemokines and inflammation-related cancer.

Two aspects of decoy receptor biology are critical to understand their role in intestinal inflammation. First, D6 does not direct a local immune response within the intestine, but instead provides a modulatory function. The chemokine scavenging activity of D6 is a delayed response, secondary to the induction of a pro-inflammatory chemokine gradient, to limit an overzealous immune response. Second, a challenge in modulating the immune response is immunosuppression, leading to opportunistic infections. However, D6 binds only pro-inflammatory chemokines, having no affinity for homeostatic chemokines. Furthermore, expression of D6 is also dependent on the chemokine gradient, being thus self-regulated. In this way, D6 deficiency does not increase susceptibility to infection, despite an inability to adequately decrease chemokine concentrations.

D6 offers a potential therapeutic strategy for the promotion of homeostasis in IBD, which would indirectly reduce the risk of colon cancer. Designing a new generation of drugs that target a dysregulated immune response, such as D6, without disturbing immune surveillance and regulatory functions remains a holy grail of immune-drug design.

**FUTURE DIRECTIONS**

The manuscript by Vetrano provides insight for a role of D6 in intestinal inflammation and opens new avenues for further investigation. A question that remains unanswered is whether colon cancer (not associated with IBD) will similarly show increased D6 expression. But most importantly, as D6 is not predominantly expressed by innate immune cells (which constitute the predominant infiltrating subset in acute DSS colitis), but rather by B cells and dendritic cells, exploring whether haematopoietic D6 might be more critical for the modulation of inflammation in models where there is larger role for the adaptive immune response (i.e. IL10−/−, TNFΔARE or SAMP1/Yit mice) is highly relevant.