

13. **Horiguchi N**, Wang L, Mukhopadhyay P, *et al.* Cell type-dependent pro- and anti-inflammatory role of signal transducer and activator of transcription 3 in alcoholic liver injury. *Gastroenterology* 2008;**134**: 1148–58.
14. **Hong F**, Radaeva S, Pan HN, *et al.* Interleukin 6 alleviates hepatic steatosis and ischemia/reperfusion injury in mice with fatty liver disease. *Hepatology* 2004;**40**:933–41.
15. **Sun Z**, Klein AS, Radaeva S, *et al.* In vitro interleukin-6 treatment prevents mortality associated with fatty liver transplants in rats. *Gastroenterology* 2003;**125**:202–15.
16. **Naugler WE**, Sakurai T, Kim S, *et al.* Gender disparity in liver cancer due to sex differences in MyD88-dependent IL-6 production. *Science* 2007;**317**:121–4.

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-1 β , 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 which the cDNA was isolated (G Graham, personal communication, 13 August 2009). In D6 the DRYLAIV motif is replaced to DKYLEIV and just one substitution to DKYLAIV restores weak signal trans-

duction capacity.⁴ D6 scavenges pro-inflammatory CC chemokines (ie, CCL2,3,4,7,8,11,13,17,22,23,24, CCL3L1) while sparing homeostatic CC chemokines, or those from other subfamilies.¹ To accomplish this, D6 constitutively shuttles to and from the cell surface via recycling endosomes. Sensitive to the low pH of endosomes, internalised chemokines are released and degraded, allowing D6 to return to the cell surface, in a process analogous to a “tapis roulant”.¹

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 sole location is not obvious, as chemokines appear sufficiently separated by intervening tissue to be scavenged by LEC D6⁵ (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 chemokine scavengers (hypothesis B). This concept is now being challenged by the work of Vetrano *et al*⁶ (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.⁶ 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 localised production of chemokines, matrix metalloproteinases and angiogenic factors which contribute to tumour progression. C–C chemokines CCL2, CCL4 and CCL5 directly induce MMP9 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,

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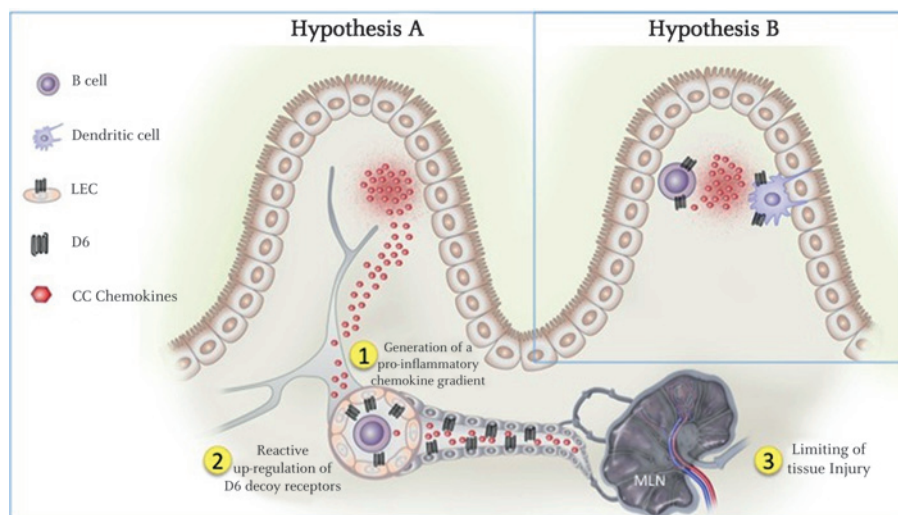


Figure 1 Alternative/complementary hypotheses for the role of D6 in intestinal inflammation. In hypothesis A, expression of D6 on lymphatic endothelial cells (LEC) is critical to prevent tissue injury due to sustained high levels of pro-inflammatory chemokines. The study by Vetrano *et al*⁶ supports this hypothesis in an acute model of colonic inflammation. In the second hypothesis, co-expression of D6 and CC chemokines on chronic inflammatory cells such as dendritic cells and B cells facilitates their localisation to the site of greatest chemokine release that results in local removal of the chemotactic stimulus. This hypothesis, though not critical in the DSS model, may reflect a role for D6 in conditions where the inflammatory infiltrate is more substantially composed of B cells and dendritic cells. In either hypothesis failure of D6 to curb pro-inflammatory chemotaxis results in exacerbation of tissue injury.

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.¹⁰ 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 (ie, IL10^{-/-}, TNFΔARE or SAMP1/Yit mice) is highly relevant.

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REFERENCES

1. Locati M, Torre YM, Galliera E, *et al*. Silent chemoattractant receptors: D6 as a decoy and scavenger receptor for inflammatory CC chemokines. *Cytokine Growth Factor Rev* 2005;16:679–86.
2. Mantovani A, Locati M, Vecchi A, *et al*. Decoy receptors: a strategy to regulate inflammatory cytokines and chemokines. *Trends Immunol* 2001;22:328–36.
3. Nibbs RJ, Wylie SM, Pragnell IB, *et al*. Cloning and characterization of a novel murine beta chemokine receptor, D6. Comparison to three other related macrophage inflammatory protein-1alpha receptors, CCR-1, CCR-3, and CCR-5. *J Biol Chem* 1997;272:12495–504.
4. Nibbs RJ, McLean P, McCulloch C, *et al*. Structure-function dissection of D6, an atypical scavenger receptor. *Methods Enzymol* 2009;460:245–61.
5. McKimmie CS, Fraser AR, Hansell C, *et al*. Hemopoietic cell expression of the chemokine decoy receptor D6 is dynamic and regulated by GATA1. *J Immunol* 2008;181:8171–81.
6. Vetrano S, Borroni E, Sarukhan A, *et al*. The lymphatic system controls intestinal inflammation and inflammation-associated colon cancer through the chemokine decoy receptor D6. *Gut* 2010;59:197–206.
7. Jamieson T, Cook DN, Nibbs RJ, *et al*. The chemokine receptor D6 limits the inflammatory response in vivo. *Nat Immunol* 2005;6:403–11.
8. Martinez de la Torre Y, Locati M, Buracchi C, *et al*. Increased inflammation in mice deficient for the chemokine decoy receptor D6. *Eur J Immunol* 2005;35:1342–6.
9. Balkwill F. Cancer and the chemokine network. *Nat Rev Cancer* 2004;4:540–50.
10. Borroni EM, Buracchi C, Savino B, *et al*. Role of the chemokine scavenger receptor D6 in balancing inflammation and immune activation. *Methods Enzymol* 2009;460:231–43.