

# Adhesion molecule shows promise for treating colitis

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The adhesion molecule CD146 plays a vital role in inflammation and offers a promising therapeutic target for treating inflammatory bowel disease (IBD) as well as preventing colitis-associated colorectal cancer, say scientists. Targeting CD146 with anti-CD146 antibody AA98, especially in combination with an anti-TNF-alpha antibody, showed promising results in mice. Their report is published in *The American Journal of Pathology*.

Enhanced CD146 expression has been reported on endothelial cells in intestinal biopsies from patients with [inflammatory bowel disease](#). There have also been clinical observations that CD146 expression is associated with other inflammatory diseases such as rheumatoid arthritis, chronic renal failure, and diabetes. However, the mechanisms were unclear until now.

In the present study, the investigators set out to examine how CD146 functions in [inflammatory diseases](#) and, more importantly, to understand its role in chronic-inflammation-associated carcinogenesis. They found that overexpressed endothelial CD146 promoted the inflammatory responses in IBD, which further potentiated the occurrence of colitis-associated carcinogenesis (CAC). "Eliminating endothelial CD146 by conditional knockout in two different mouse models of colitis significantly reduced the severity of inflammation and decreased tumor incidence and tumor progression in a mouse model of CAC," reports lead investigator Xiyun Yan, PhD, from the Key Laboratory of Protein and Peptide Pharmaceuticals, Institute of Biophysics, Chinese Academy

of Sciences, Beijing.

To mimic the long-lasting and relapsing property of IBD, the team also established a chronic colitis mouse model and administrated an anti-CD146 antibody, AA98, after the onset of disease. Because IBD is a clinically heterogeneous disease with complex mechanisms, a combination of drugs targeting distinct biomarkers might be considered as a potential approach. Thus, they also tested the combined treatment of anti-CD146 antibody AA98 and anti-TNF-alpha antibody V1q in this model. Disease activity index and histological score were dramatically reduced in the AA98 treatment group and the V1q treatment group, especially the combination treatment group, compared with the mIgG treatment group.

"Current IBD treatment mainly focuses on inhibition of cytokines. Infliximab, an antibody against TNF-alpha, has been approved by the US Food and Drug Administration for treating ulcerative colitis (UC), and many inhibitors and antibodies against TNF-alpha are now under clinical evaluation. However, side effects such as increased risk of infection and even lymphoma have been indicated. Moreover, clinical trial data suggest that a considerable proportion of patients receiving anti-TNF-alpha therapy may become resistant to treatment in the first few years. Anti-adhesion molecule therapy could therefore be an alternative therapeutic intervention," explains Dr. Yan.

The investigators also found that there was a decrease in blood vessels and lymphocytic cell infiltration, both in AA98-treated and V1q-treated mice, whereas a more significant decrease was observed in the combination treatment group. The expression levels of proinflammatory cytokines were also reduced.

"Our study provides the first evidence that endothelial CD146 plays a dual role on endothelium, facilitating leukocyte extravasations and

angiogenesis, thus promoting inflammation," says Dr. Yan. "Its involvement in the recruitment of inflammatory lymphocytes and promotion of angiogenesis may serve as a critical link between colitis and CAC. Although far more work needs to be done before bringing it to the clinic, targeting CD146 with AA98, especially in combination with an anti-TNF-alpha antibody, may be a therapeutic option in treating colitis, as well as a preventative method for CAC."

There is growing evidence that chronic inflammation contributes to carcinogenesis, including gastrointestinal, lung, and prostate cancers. Patients suffering from UC, a major form of IBD, for more than 10 years are six to ten times more likely to develop colorectal cancer than the general population. UC is characterized by a long-lasting cycle of remission and exacerbations of ulceration of bowels, abdominal pain, diarrhea, bloody stool, and other systemic symptoms.

**More information:** "Targeting endothelial CD146 attenuates colitis and prevents colitis-associated carcinogenesis," by Shu Xing, Yongting Luo, Zhihua Liu, Pengcheng Bu, Hongxia Duan, Dan Liu, Ping Wang, Jing Yang, Lina Song, Jing Feng, Dongling Yang, Zhihai Qin, and Xiyun Yan [dx.doi.org/10.1016/j.ajpath.2014.01.031](https://doi.org/10.1016/j.ajpath.2014.01.031) , published in *The American Journal of Pathology*, Volume 184, Issue 5 (May 2014)

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