It is thought that targeting selectins may be a valuable target to induce DKO. Inflammatory bowel disease (IBD) is characterized by excessive recruitment of circulating leukocytes to the intestinal lamina propria leading to a hyperactive inflammatory response.

This inflammatory response leads to a number of unsatisfactory side effects including severe diarrhea, abdominal pain, reduced appetite, blood in stool, and unintended weight loss as well as potentially life threatening complications such as bowel perforations and toxic megacolon (Hanauer, 2006 and Loftus, 2004).

Circulating leukocytes attach to the intestinal tissues by way of cell adhesion molecules (CAMs) P-selectin and E-selectin, which are upregulated on intestinal tissue during inflammation, and their respective ligands on the leukocytes P-selectin glycoprotein ligand-1 (PSGL-1) and CD44 (Angiari, 2015).

It has been shown that P-selectin creates the initial connection which begins to slow the leukocytes and E-selectin is responsible for slowing the leukocytes even further, eventually stopping them in a process known as margination (Hidalgo et al., 2007).

It is thought that targeting selectins may be a valuable target to treat autoimmune disorders such as IBD, and in previous studies blocking each selectin individually resulted in marked decreases in inflammation associated with inflammation of the bowel. However, the effect of blocking both molecules together remains unknown.

The goal of this proposal is to examine the effect of blocking PSGL-1 and CD44 in vivo. The hypothesis would fail to be rejected if the data from the two groups are in fact different.

Methods

40 BALB/c mice

Expected Results

• It is expected that in vitro assays will confirm binding of antibodies to their appropriate target molecules and that the DKO mice are in fact deficient of both PSGL-1 and CD44.

• It is expected that mice induced with colitis but not given an inhibitory treatment will have the greatest number of adherent leukocytes as determined by IVM and largest histological damage score.

• Mice induced with colitis and treated with the monoclonal antibodies will have the second highest number of adherent leukocytes and histological damage score.

• The group of DKO mice induced with colitis and the group not treated or induced will have similar, not significantly different number of adherent leukocytes.

• However, it is expected that the DKO and non-induced mice will have similar histological damage scores with both having a score of "0".

Conclusion

• The hypothesis would fail to be rejected if the data from the two groups with PSGL-1 and CD44 inhibited was significantly different from the data collected on the mice induced with colitis but did not have any CAM inhibition.

Literature Cited


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