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The Role Of The Stem Cell Marker CD24 During The Healing Phase Of Inflammatory Bowel Disease

Lay Summary

Aims: To investigate how CD24 may facilitate tissue healing in the intestine

Background:

Inflammatory Bowel Disease (IBD) encompasses a variety of diseases. The most common types of IBD are Crohn's Disease (CD) and Ulcerative Colitis (UC). These are distinct entities but both diseases are characterised by repeated episodes of inflammation. The power of the gut to heal the damage caused by acute episodes of inflammation are remarkable and frequently the mucosal architecture reverts to normal. However, the healing response itself may become aberrant and result in pathological changes (such as strictures or fibrosis). This occurs most commonly when healing is delayed or when there are frequent cycles of inflammation/healing. Current therapies in IBD are based on reducing inflammation to allow the healing process to occur. However, better understanding of the healing process in the bowel may allow interventions which will accelerate normal healing and possibly prevent abnormal healing.

CD24 is a small molecule which is attached to the cell membrane. Although originally described as a molecule involved in cell adhesion, it has more recently been reported to be a marker of stem cells in the colon. It is also thought that it can confer resistance to apoptosis (programmed cell death) and, in the normal colon, CD24 expression is seen only in the base of the crypts where the stem cells are thought to be located.

During the inflammatory phase of IBD, the normal mucosal tissue is destroyed. The healing process involves replacement of damaged tissues by health new cells generated from the residual tissue. We have found that CD24 expression is up-regulated in regenerative tissues in both CD and UC. This is most probably represents an expansion of the stem cell compartment in response to the need to produce new tissue. We have shown that, *in-vitro*, inducing expression of CD24 in cell lines will (a) increase cell numbers and (b) stimulate cell migration.

Experimental plan:

Our data suggest that CD24 may be involved in tissue healing in the gut and, as a cell surface molecule, it may be easier to manipulate than molecules located within the cell. Almost nothing is known about the mechanisms through which CD24 acts and this project will aim to:

- (i) Identify the downstream signalling molecules involved in transmitting the CD24 signal.
- (ii) Identify downstream target genes especially other genes involved in maintaining stem cells.
- (iii) Evaluate the role of CD24 in inhibition of apoptosis.
- (iv) Evaluate the mechanism through which CD24 can stimulate cell migration.
- (v) Delineate the target genes involved in healing in IBD

This study is ambitious for a two year project. However, it is feasible since much technical preparatory work has been done during the process of accruing preliminary data. Thus CD24 has been cloned and successfully shuttled into an expression vector. All the techniques to be used in the project are well established in the host lab. It is anticipated that once the project is complete, our understanding of the role that CD24 may play during tissue healing will be greatly enhanced.