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EDITORIAL

Mitochondria in Ulcerative Colitis

Energy deficiency as a possible contributor to pathogenesis of ulcerative colitis (UC) is an old story lacking molecular detail. The paper by Sünderhauf et al[1] in this issue of *Cellular and Molecular Gastroenterology and Hepatology* has the potential to fill this gap by focusing on the importance of mitochondrial oxidative phosphorylation in differentiating goblet cells. It is noteworthy that the likely culprit cell in ileal Crohn's disease, the Paneth cell,[2] also displays a mitochondrial impairment.[3] In both types of secretory cells, blocked differentiation may act as a relevant disease mechanism.[2,4]

Sünderhauf et al[1] found that in UC patients in remission low p32, a factor maintaining oxidative phosphorylation, was instrumental in decreasing goblet cell differentiation. The link was confirmed in cultured cells mimicking some goblet cell functions by p32 silencing. Similarly, the coordinate regulation of p32 expression and goblet cell function was confirmed in a mutant mouse model. On top of these links, they succeeded in finding a "remedy" in form of a glucose-free, protein-rich diet (in animals; humans may find it unpalatable).

In this field, the key to finding "primary" events is to look into noninflamed tissue, otherwise epiphenomena of inflammation may abound. It was therefore wise to use only patients in remission. It might be interesting to also look at subtotal UC as an opportunity to investigate noninvolved proximal parts of the colon, likely to develop disease later following progression. A hidden jewel in their data is the association of azathioprine treatment with induced p32, possibly an unexpected novel mechanism of action in maintaining remission.

The link of low p32 and impaired goblet cell differentiation fits nicely in the concept of UC as a barrier disease: goblet cells forming the 2 mucus layers protecting the epithelium are known to be diminished and less functional (differentiated), leading to a thin and less consistent mucus in UC.[5] Because only intact mucus binds sufficient defensins in a reversible fashion, it is obvious that in this disease the first-line antibacterial barrier is compromised. As a consequence, bacterial invasion may ensue, prompting the bacterial-driven immune response damaging the mucosa. Interestingly, based on single-cell studies, alterations of epithelial cell diversity in UC have recently been described, with a positional remodeling that is linked to downregulation of WFDC2, another antibacterial factor.[6]

Based on the complexity of diffentiation factors, such as KLF4 and notch and others, further studies are required to understand the details of the interactions with metabolic and nutritional factors. The recently published paper by Ludikhuize et al[7] gives some interesting signaling background in ileal mucosa, suggesting that foxo and notch interact. Their inhibition induces mitochondrial fission. Mitochondrial fission may be a requisite for stem cell differentiation into Paneth and goblet cells.

Taken together and considering where we come from (a T-cell disease), these are exciting developments and the work presented by Sünderhauf et al[1] has the chance to become a classic. It may seem far-fetched but there is at least light at the end of the tunnel leading to a causative therapy, although it is probably not the diet mentioned previously.

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Conflicts of interest
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