OxyUC

Title The impact of hypoxia on inflammation and tumorigenesis in ulcerative colitis.

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Project partners

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Abstract Ulcerative colitis (UC) is a debilitating intestinal inflammatory disorder affecting approximately 1:200 people, the prevalence of which is disproportionately high in Europe. As well as experiencing severe clinical symptoms, 10-18% of UC patients develop inflammation-associated colon cancer. The molecular mechanisms underpinning both the pathology and increased risk of cancer in UC patients remain unclear and effective treatment is a clearly defined clinical need. It recently became clear that the microenvironment in UC significantly impacts inflammation and tumor progression via the promotion of immune, angiogenic and metabolic processes. We will test the hypothesis that the microenvironment (specifically tissue hypoxia) is a key determinant of mucosal inflammation and the risk of developing colon cancer in UC patients. Hypoxia is a feature of the intestinal mucosa during UC. Hydroxylases are oxygen-sensing enzymes which control the transcriptional response to hypoxia through regulating the hypoxia-inducible factor (HIF). Our previous work using a

systems biology approach, informed by iterative mathematical modeling and biological experimentation implicated the HIF pathway as a key signaling hub during chronic inflammation. Based on this, we hypothesize that the degree and duration of mucosal hypoxia experienced by UC patients is a key driver of disease progression. In this proof of concept study for systems medicine, we will use pre-clinical and clinical approaches integrated with computational biology and previously generated mathematical models informed by clinical measurements to investigate the relationship between tissue hypoxia / HIF activation and inflammation / tumor development in UC patients. The successful completion of this programme will allow us to promote personalized prevention, diagnostics and treatment regimens for UC patients based on an understanding of the individual micro-environmental features of their disease.

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