New therapeutic targets for tumours associated with chronic inflammation

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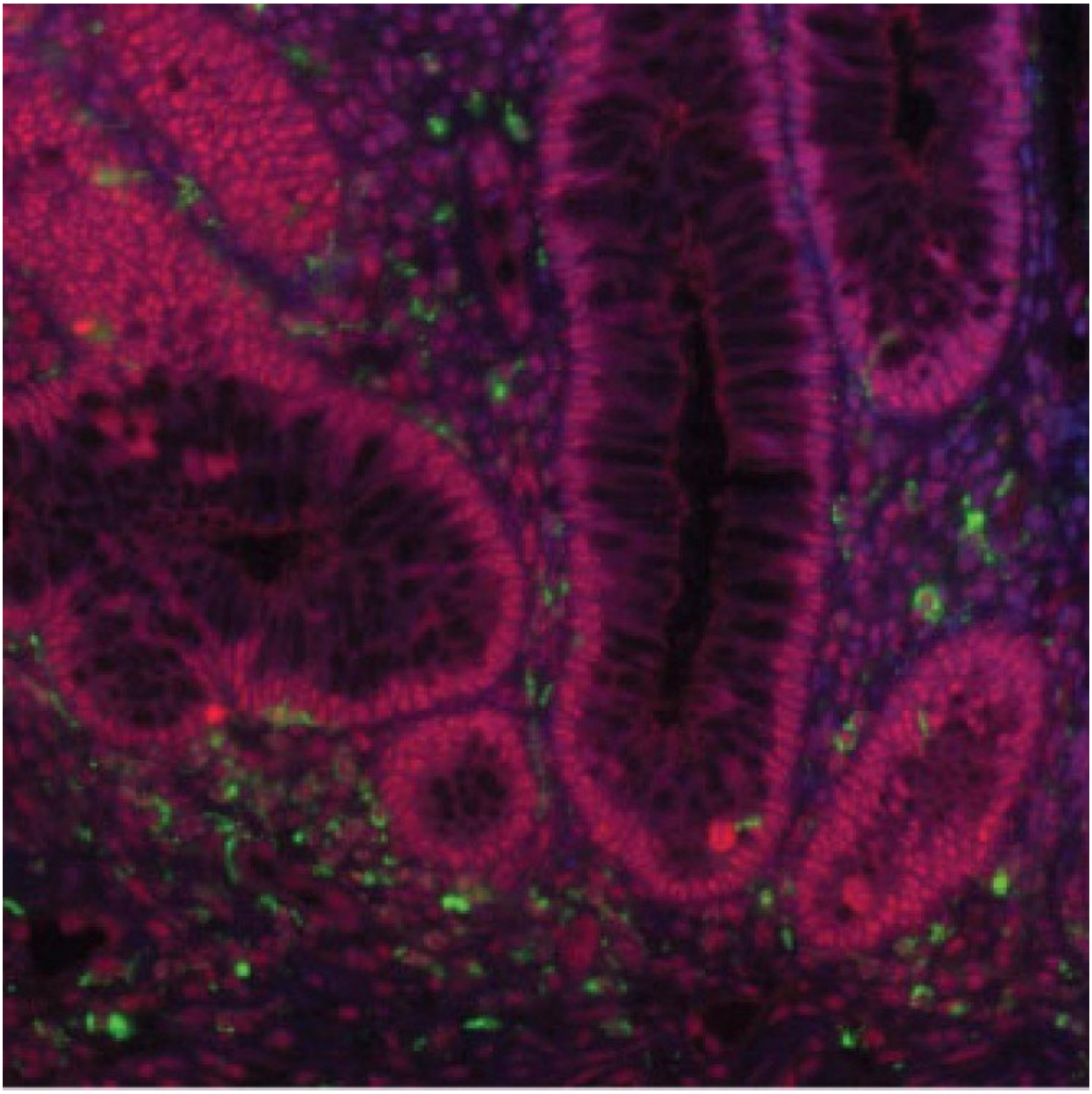


Bowel of a patient with Ulcerative Colitis, a chronic inflammatory bowel disease. In green: macrophage marker, in red: activated p38 protein, in blue: nucleus. Credit: Catrin Youssif, IRB Barcelona.

Scientists headed by ICREA researcher Angel R. Nebreda at the Institute for Research in Biomedicine (IRB Barcelona) report a new mechanism that contributes to the development of inflammation-associated colon cancer and points to new therapeutic targets. The study has been published in the journal *EMBO Molecular Medicine*.

More than 1 million people worldwide are diagnosed with colon cancer every year. Although many of these cases are spontaneous, chronic inflammation is one of the main causes underlying the development of this disease.

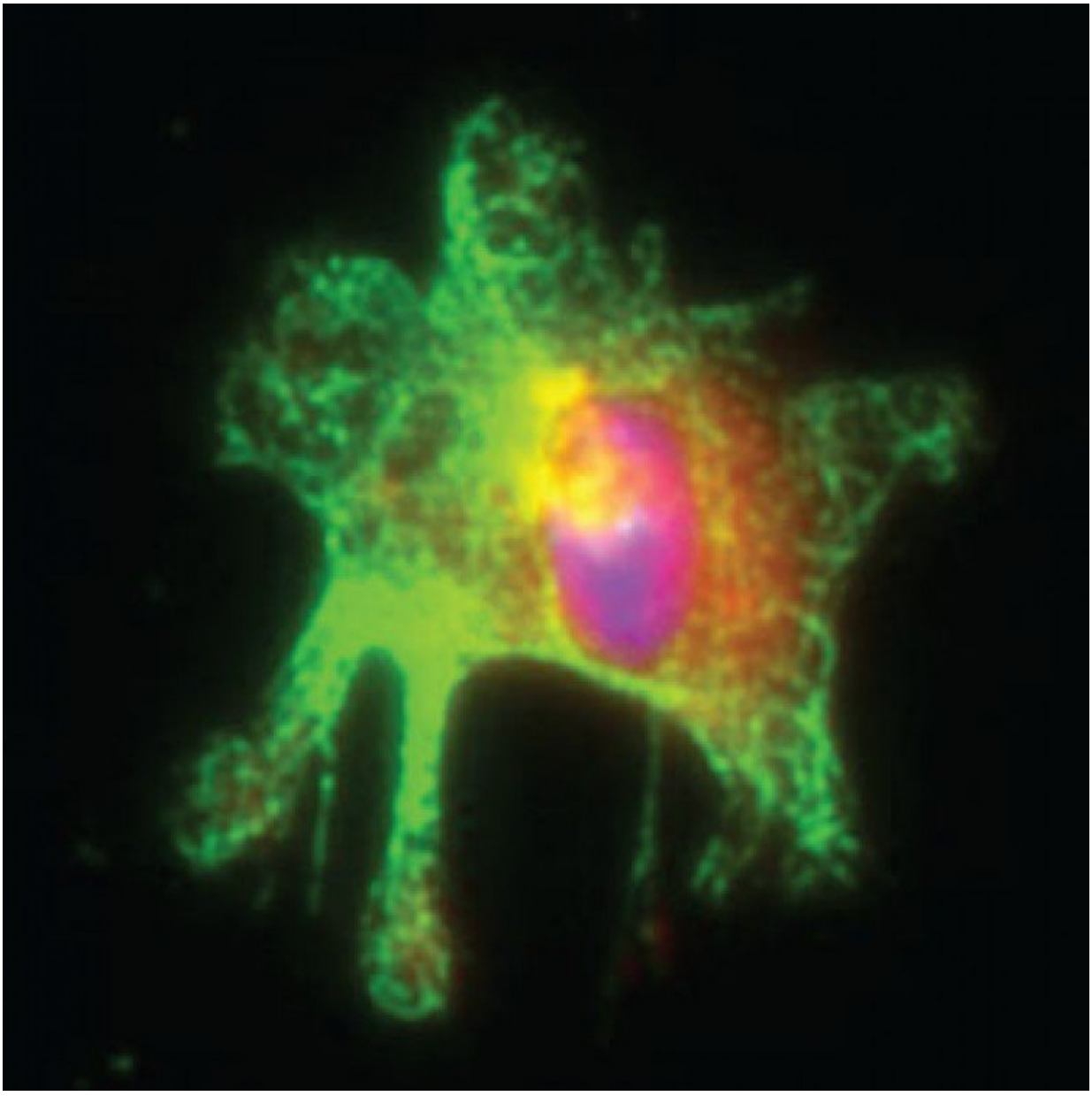
"Our study demonstrates that the capacity of myeloid cells to enhance tumorigenesis is determined by the protein p38. In particular, we have identified an important contribution of the hormone IGF-1, which is activated by p38 in myeloid cells", explains Nebreda, head of the Cell Sigalling and Cell Cycle lab.

The research has been done using models of acute and chronic inflammation in genetically modified mice or in mice treated with pharmacological inhibitors.

IGF-1 and inflammation

IGF-1, a hormone similar to insulin, emerges as a potential therapeutic target— preferably in combination with prior detection of inflammatory infiltration in biopsies of patients and levels of IGF-1—in intestinal diseases associated with inflammation. This finding could help to

address the low success rate achieved by pharmacological inhibitors of p38 in clinical trials in patients with intestinal inflammatory disease who are predisposed to colon cancer.

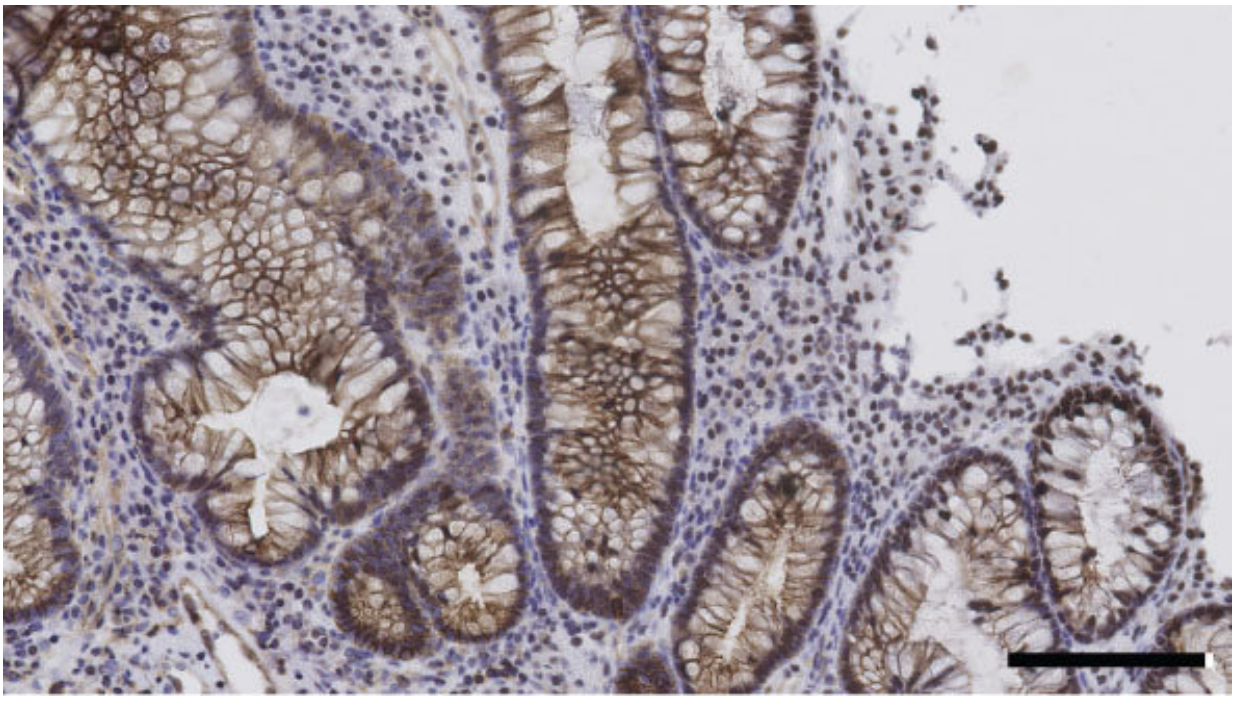


Activated macrophage isolated from mouse intestine. In green: macrophage marker, in red: inflammation marker (iNOS), in blue: nucleus. Credit: Catrin Youssif, IRB Barcelona

"We found that p38 inhibition specifically in myeloid cells protects mice against inflammation-associated colon cancer, and this protective effect is associated with a reduced production of chemokines, which are crucial for the recruitment of cells from the immune system", explains CatrinYoussif, first author of the study and current alumnus of IRB Barcelona.

The study demonstrates that the genetic or pharmacological inhibition of IGF-1 suppresses the recruitment of inflammatory cells and reduces the burden of colon cancer tumours associated with inflammation.

"On the basis of our findings, we propose that decisions regarding therapy should take into consideration the inflammatory conditions and the levels of IGF-1 in biopsies of patients with inflammatory intestinal diseases or colitis-associated cancer," conclude the authors of the study.



Bowel of a patient with Ulcerative Colitis, a chronic inflammatory bowel disease. In brown: activated IGF1 receptor, in blue: nucleus. Credit: Catrin Youssif, IRB Barcelona

More information: Catrin Youssif et al. Myeloid p38α signaling promotes intestinal IGF-1 production and inflammation-associated tumorigenesis, *EMBO Molecular Medicine* (2018). DOI: 10.15252/emmm.201708403

Provided by Institute for Research in Biomedicine (IRB Barcelona)