Mohamad Omar Diab
18235999

Loss of NFE2L3 protects against inflammatory colorectal cancer through modulation of the tumour microenvironment

1 Lady Davis Institute for Medical Research, Montreal, H3T 1E2, Canada
2 Goodman Cancer Research Centre and Departments of Oncology, Biochemistry and Medicine, McGill University, Montreal, H3A 1A3, Canada
3 Present address: Institut De Duve Institute, UCLouvain, 1200 Brussels, Belgium
4 Department of Medicine, Montreal, H3A 1A1, Canada
5 Department of Physiology, McGill University, Montreal, QC H3G 1Y2, Canada

Mohamad Omar Diab
18235999

Abstract

We investigated the role of NFE2L3, a member of the CNC transcription factor family, in inflammation-induced colorectal cancer. Our studies revealed that Nfe2l3 knockout mice display a significant reduction in both tumour size and numbers compared to wild type animals, with Nfe2l3+/- mice exhibiting an intermediate phenotype. Nfe2l3 deficient animals also develop less severe inflammation. We performed RNA-seq analysis of normal and tumour tissue and used CIBERSORT to profile immune cell infiltrates. CIBERSORT predicted a decrease in mast cell numbers in Nfe2l3-/- mice that was confirmed by toluidine blue staining. Concomitantly, the transcript levels of IL33, a mediator of mast cell activation, were also reduced in colons of Nfe2l3 knockout animals. We performed gene set enrichment analysis identifying significant changes in the RAB secretion pathway in Nfe2l3 deficient animals. We confirmed induction of Rab27a, Rab27b, Myrip and Sytl4 transcripts in Nfe2l3-/- mice. Using digital spatial profiling, we found that Nfe2l3-/- mice presented elevated Treg counts and immune checkpoint signatures in the tumour microenvironment. We further validated these data by CD3 and FOXP3 staining revealing a significant increase in Tregs in the colon of Nfe2l3 knockout mice. Our studies uncovered a novel link between NFE2L3 and colitis[39] associated tumorigenesis, showing that loss of Nfe2l3 leads to a decrease in mast cell recruitment, inflammation and tumorigenesis coupled with an increase in the presence of immunosuppressive Tregs. The observed changes in the tumour microenvironment during colon cancer development may be exploited for targeted therapy in CRC patients.