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The impact of tofacitinib and budesonide on stemness, cell death, and chemokine release in IBD patient-derived colonoids

Arun Sridhar[1, 2], Ingunn Bakke[1,3], Shreya Gopalakrishnan[1], Nimo Mukhtar Mohamud Osoble[1], Emilie Prytz Hammarqvist[1], Henrik P Sahlin Pettersen[1,3,4], Arne K. Sandvik[1,2], Ann Elisabet Østvik[1,2], Marianne Doré Hansen[1,3] & Torunn Bruland[1,2]

Contact: arun.sridhar@ntnu.no

CAG-IBD Precision medicine in Inflammatory bowel disease

ST. OLAVS HOSPITAL UNIVERSITETSSYKEHUSET I TRONDHEIM

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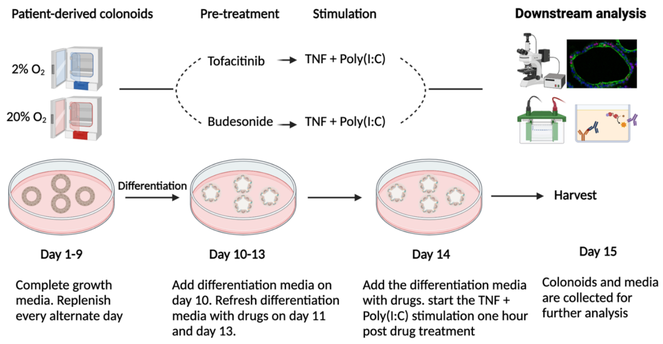
INTRODUCTION

Inflammatory bowel diseases (IBD) are chronic conditions with alternating periods of symptom-free remission and symptomatic flare-ups. Treatments for IBD therefore include both induction therapy aimed at reducing inflammation, alleviating symptoms, and achieving remission, and maintenance therapy to sustain remission and prevent relapses. Until now, our understanding of how most IBD drugs developed to modulate immune cells impact intestinal epithelial cells has been limited, particularly regarding mechanisms related to promoting mucosal healing and maintaining remission. Our hypothesis is that mechanisms of action (MOA) of IBD drugs in intestinal epithelium are relevant for homeostasis and will vary for, e.g., targeted small molecules and broad-spectrum first-line corticosteroids. Human colon organoids (colonoids) recapitulate important features of colonic epithelium in a donor-specific manner. Here, we use colonoids from healthy donors and IBD patients to elucidate MOA for budesonide and the pan-JAK inhibitor tofacitinib, especially their different impacts on stemness in differentiated colonoids.

METHODS

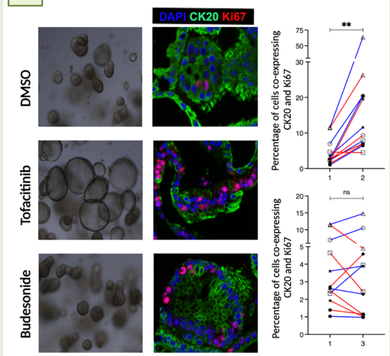


The experimental protocols used in the presents study **mimics maintenance/preventions treatment in 2% (physioxia) and 20% (hyperoxia) oxygen concentration.**

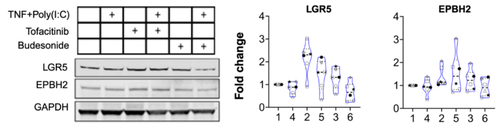
- we analyzed drug-effects on colonoids cultivated in uninflamed conditions.
- we analyzed whether the two drugs could prevent or attenuate inflammatory responses upon pro-inflammatory stimulations with TNF/Poly(I:C)

RESULTS

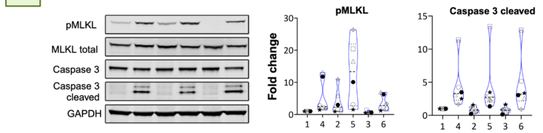
1 Growth



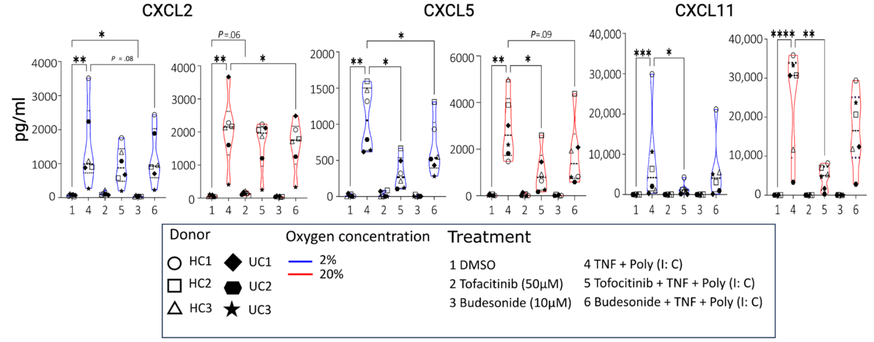
2 Stemness



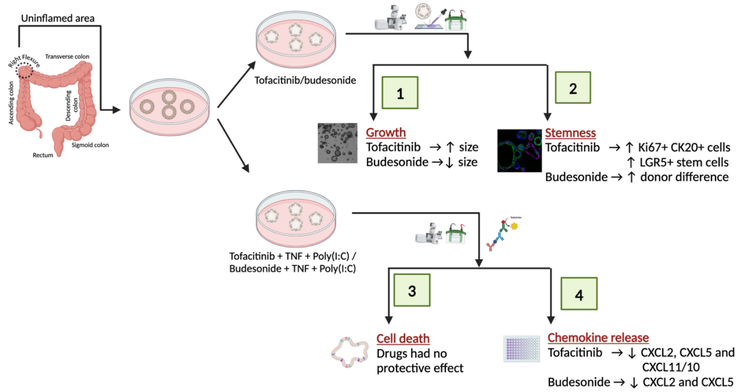
3 Cell death



4 Chemokine release



CONCLUSION



1,2 Tofacitinib led to an increase, and budesonide resulted in a decrease in colonoid size. Tofacitinib treatment increased co-expression of CK20 and Ki67 cells and enhanced expression of the stem cell marker LGR5. Budesonide treatment did not seem to have a consistent effect o proliferation or stemness.

3 Neither tofacitinib nor budesonide pre-treatment showed definite harmful or protective effects on TNF+Poly(I:C) induced cell death in colonoids

4 Both drugs attenuated TNF+Poly(I:C) induced chemokine release of CXCL2, CXCL5 and CXCL11 from colonoids.

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[1]Department of Clinical and Molecular Medicine (IKOM), NTNU - Norwegian University of Science and Technology, Trondheim, Norway
[2]Department of Gastroenterology and Hepatology, Clinic of Medicine, St. Olav's University Hospital, Trondheim, Norway
[3]Clinic of Laboratory Medicine, St. Olav's University Hospital, Trondheim, Norway
[4]Department of Pathology, St. Olav's University Hospital, Trondheim, Norway