An IBD associated variant in PTPN2 promotes inflammatory responses but enhances the anti-inflammatory effect of Spermidine

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Protein tyrosine phosphatase non receptor 2 (PTPN2)

- SNP rs1893217 in PTPN2 gene associated with inflammatory diseases
- Clinical relevance: more severe disease, but
- Better response to TNF-inhibitors

Spermidine

Polyamine: Monoaminopropylputrescine

- Potent activator of PTPN2
- Limits IFN-γ induced pro-inflammatory signaling

- Mouse model:
  - Promotes intestinal barrier function
  - Reduces intestinal inflammation

What is the effect of spermidine in human cells?

Scharl et al. Gastroenterology 2009; Scharl et al. GUT 2011; Spalinger et al. Digestion 2016; Moron et al, PloSOne 2013; Penrose et al. JBC
Methods

- Isolation of **human PBMC** from Healthy controls (HC) and IBD patients
  - either WT (TT) or heterozygous (CT) for SNP rs 1893217
  - Treatment with **INF-γ** and/or **spermidine** for 24h
- Isolate mRNA and analyze **IFN-γ target gene** expression
Spermidine reduces IFN-\(\gamma\) induced gene expression

Increased IFN-\(\gamma\) response in heterozygous (CT) patients

HC: healthy control; CT: heterozygous; TT: WT for SNP rs1893217
Better response to spermidine in variant carriers

Pronounced reduction upon spermidine treatment in heterozygous (CT) patients

HC: healthy control; CT: heterozygous; TT: WT for SNP rs1893217
Summary and Conclusion

- Spermidine reduces IFN-γ signaling
- PTPN2 variant promotes IFN-γ response
- Variant enhances responsiveness to spermidine
- Variant might be a predictor for treatment response

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