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T-regulatory cells in colon cancer.

Friend or Foe?
Increased frequency of regulatory T cells in peripheral blood and tumour infiltrating lymphocytes in colorectal cancer patients

Khoon Lin Ling1, Sarah E. Pratap1, Gaynor J. Bates2, Baljit Singh3, Neil J. Mortensen3, Bruce D. George3, Bryan F. Warren4, Juan Piris4, Giovanna Roncador5, Stephen B. Fox2, Alison H. Banham2 and Vincenzo Cerundolo1

Intraepithelial Effector (CD3+)/Regulatory (FoxP3+) T-Cell Ratio Predicts a Clinical Outcome of Human Colon Carcinoma

FRANK A. SINICROPE,*,† RAFAELA L. REGO,*,‡ STEPHEN M. ANSELL,§ KEITH L. KNUTSON,‖ NATHAN R. FOSTER,‖ and DANIEL J. SARGENT‖
Antigen-specific Tregs control T cell responses against a limited repertoire of tumor antigens in patients with colorectal carcinoma

Andreas Bonertz,1 Jürgen Weitz,2 Dong-Ho Kim Pietsch,1 Nuh N. Rahbari,2 Christoph Schlude,1 Yingzi Ge,1 Simone Juenger,1 Israel Vlodavsky,3 Khashayarsha Khazaie,4 Dirk Jaeger,5 Christoph Reissfelder,2 Dalibor Antolovic,2 Maximilian Aigner,2 Moritz Koch,2 and Philipp Beckhove1

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- 5-10% of total “naïve” CD4 T cells.
- positively selected in the thymus
- CD25⁺ (IL2Rα subunit)
- FOXP3⁺
- potent suppressors of antigen specific CD4 and CD8 T cell responses

- potent suppressors of inflammation
Tumor-Infiltrating FOXP3\(^+\) T Regulatory Cells Show Strong Prognostic Significance in Colorectal Cancer

Paul Sakama, Michael Phillips, Fabienne Griev, Melinda Morris, Nik Zeps, David Joseph, Cameron Platell, and Barry Iacopetta

Conclusion

FOXP3\(^+\) Treg density in normal and tumor tissue had stronger prognostic significance in colorectal cancer compared with CD8\(^+\) and CD45RO\(^+\) lymphocytes. The finding of improved survival associated with a high density of tumor-infiltrating FOXP3\(^+\) Tregs in colorectal cancer contrasts with several other solid cancer types. The inclusion of FOXP3\(^+\) Treg density may help to improve the prognostication of early-stage colorectal cancer.

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Tall, hyperchromatic disorderly cells with cigar-shaped nuclei and concomitant crypt budding, and absence of sulfomucin expressing goblet cells
Treg transfer suppresses cancer associated inflammation
Adoptive Transfer of Healthy Treg
Transfer of $10^5$ Treg: 4 weeks
What about the endogenous Treg
Treg in healthy mice < Treg in polyp mice
Treg are altered in polyposis

- IL17
  - healthy
  - polyp
- IL10
  - healthy
  - transferred
  - endogenous

Foxp-3

Bar chart showing % IL10
Adoptive Transfer in Rag$^{-/-}$ mice

- Healthy donor
- Polyp-ridden donor
ΔTreg have TH17 characteristics (RORγT)

Gated on CD4⁺Foxp3⁺IRF4⁺
Cytokine milieu found in tumor lysates of CRC patients

Increase in TGFβ, IL6 & IL1β supports IL17 conversion
Treg from colon cancer patients are pro-inflammatory.
Human Treg

CD45RA vs. Foxp3

HD PB

CRC PB

CRC Normal

CRC Tumor
DC and Treg plasticity

(Activated Treg)
CD44
CD69
CD62L

Soluble factors??
Activation
Proliferation

nTreg

ΔDC
MC

ΔTreg

ΔDC
MC

Tumor
nTreg

Soluble factors??

Activation
Proliferation

Tumor-bearing host

DC and Treg plasticity

EARLY

(Activated Treg)
CD44
CD69
CD62L

nTreg

ΔDC

MC

ΔTreg

LAT

EARLY

ΔDC

ΔTreg

DC

nTreg

Tumor
DC and Treg plasticity

**EARLY**

(Activated Treg)

CD44
CD69
CD62L

\[ \text{DC and Treg plasticity} \]

\[ \text{tumor-bearing host} \]
Pro-inflammatory T-regulatory Cells in Colon Cancer.

• Specific Aim 1: Does the presence of “pathogenic” (pro-inflammatory Treg) in tumor correlate with clinical outcome?

• Specific Aim 2: Do Treg pro-inflammatory properties segregate in different Treg sub-populations and are they reversible?

• Specific Aim 3: What is the Gene Transcription Signature of CD4+Foxp3+ Treg in human colon cancer.