T regulatory cells in chronic inflammatory response syndrome from water-damaged buildings (CIRS-WDB)

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What are regulatory T cells ?

- T lymphocytes; “T regs”
  - Thymus derived
  - Induced by TGF beta-1
- Suppress autoimmunity
- Suppress inflammation
- CD4+CD25+ markers
- FoxP3 as additional marker

Plasticity of T regs

- Hot topic in immunology
  - Literature is still evolving
- Conversion to Th 17
- Conversion to T memory cells
- FoxP3+ and FoxP3- cells
- Role of TGF beta-1 and presence of
  - IL6 leads to TH 17
  - ROR leads to T reg

Pathogenic T cells from T regs?

- Cellular basis of innate immunity!
- Potential to intervene in autoimmunity
- Potential to affect chronic inflammatory response syndromes
- Benefit from disease modulating drugs (especially MS and RA)

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T regs in chronic illness

- Low levels in Post-Lyme, MS, RA, commensal staphylococcal infections, ciguatera, miscarriage, pre-eclampsia
- High levels in normal pregnancy
- Induced by interferon 1 beta, VIP, methotrexate and erythropoietin
- Lowered by IVIG, prednisone
- Do levels change after exposure to interior environment of water-damaged buildings (WDB)?

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Hypotheses

- Low levels of T regs are seen in untreated CIRS-WDB
- Higher levels are obtained after treatment of CIRS-WDB
- Acute illness is associated with a fall in T regs; levels rise with treatment and re-Rx
- Treatment with vasoactive intestinal polypeptide (VIP) will further increase T reg levels

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The study-1

- 350 patients treated in one clinic
- Exposure to WDB confirmed
  - Water intrusion and visible mold
  - Speciated filamentous fungi
  - All patients met GAO case definition
- Followed prospectively from baseline
  - Acute re-exposures documented
  - Chronic care

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Methods

- Flow cytometry from Quest
  - Panel included CD4+; CD25+; and CD4+CD25+
- Insurance coverage
- No commercial FoxP3 assay
- Whole blood, refrigerated
- Not possible to use library of frozen specimens

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Results-1

- Controls mean 21.3
- Cases baseline untreated 14.7
  - Adults 14.9
  - Peds 7.9
- Cases treated 21.2
- Relapse; previously treated 9.8
- Deliberate re-exposure 8.6
- After VIP 24.8

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Sequential testing

- Controls no change
- Treated cases no change
- Monitoring over time identified 6 patients with unexplained fall
- Re-investigation of these identified WDB previously unsuspected

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Deliberate re-exposure off meds

- Sequential Activation of Innate Immune Elements (SAIIE)
- Fall of T regs occurred on Day 1
- Levels did not spontaneously resolve
- Too few cases to clearly demonstrate link to TGF beta-1
- No data in literature on change in T regs from exposures

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Conclusions-1

- Use of T regs adds additional marker for defining innate immune mechanisms in CIRS-WDB
- Baseline low levels are not diagnostic as a stand-alone test
- Treatment drives up T reg levels
- T regs fall in acute re-exposure
- VIP dramatically improves levels

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Conclusions-2

- Weaknesses
  - No FoxP3 assay
  - Can't measure tissue levels
  - Can't identify pathogenic T cells
- Future use of T reg assays
  - Correlate with HLA DR
  - Expand use to multiple clinics
  - Identify mechanisms of acute and chronic changes

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