Regulatory T cells, do they fulfill their promise?

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The immune system is a delicate balance

Defense against microorganisms

Tolerance

Suppression
Treg history: Suppressive T cells

BMT

Long term full chimera BM recipient.

DLI

Sensitize d DLI

DLI

No GVHD

Weiden, P.L., Storb, R., JI, 1976
Treg history: Regulatory T cells

CD39

Sakaguchi S et al., JI, 1995
Hori S et al., Science, 2003
Fontenot J et al., Nat Immuno, 2003
Khattri R et al., Nat Immuno, 2003
1. Treg Biology
Treg development

Josefowicz SZ, Immunity, 2009
Treg suppressive function

Vignali DA, Nat Rev Immuno, 2008
Treg suppressive function: CTLA4

Qureshi OS et al, Science, 2011
Treg homeostasis

IL-2 is indispensable for Treg survival

Malek TR, Immunity, 2010
IL-2 signaling

Conventional T cells

IL-2 binding activates Jak1, Jak3, and STAT5, leading to the activation of IP3K, AKT, and mTOR. The PTEN pathway is also involved, regulating the MAPK pathway.
Treg and epigenetics


Demethylation of conventional T cells

Ohkura N et al, Immunity, 2012
Treg

- Derived from the thymus (nTreg) or peripheral induced (iTreg).
- Multiple immunosuppressive mechanisms.
- Antigen presenting (TCR) and IL-2 dependent homeostasis.
- Resistant to rapamycin.
- Specific hypomethylation pattern.
2. Treg in Primary Immunodeficiency Disorders
IPEX Syndrome

Immune dysregulation, Polyendocrinopathy, Enteropathy, X-linked.

• Defect in FoxP3, no Treg (Xp11.23)
• Clinical presentation:
  – Severe diarrhea
  – Eczema
  – Endocrinopathy (type I diabetes, thyroiditis)
  – Other autoimmune diseases
  – Infections
• Poor survival (less than 2 years)
• Treatment: multiple immunosuppressive therapies/ HSCT

TeBaud O et al., NEJM, 2001
IPEX-like Syndrome

IL2Ra (CD25) deficiency

Stat5b deficiency

Caudy AA et al, JACI, 2007
Wiskott-Aldrich Syndrome

Mixed cellular and humoral primary immunodeficiency disorder (Xp11.23)

-Triad: RECURRENT INFECTIONS
MICROTHROMBOCYTOPENIA
ECZEMA

- Autoimmune diseases (40-70%)

-increase risk for malignancy.

-Treatment: supportive care: AB, IV lgs.
HSCT/ (gene therapy)
Defect in WASp, an important protein for the cytoskeleton organization.

Impaired Treg homeostasis

Humblet-Baron S et al, JCI, 2007
STIM-1 deficiency

Calcium sensor molecule in the ER involved in T cell activation signaling

- Combined immunodeficiency: T+B+NK+ SCID like.
- Infections
- Impaired T cell activation
- Defect in cytokine secretion
- Absence of response to vaccine

- Autoimmunity: Defect in Treg number. Lymphoproliferative disorder.
- Myopathy
- Ectodermal dysplasia

Feskea S et al, Clin Immuno, 2010
Clinical Treg deficiency

FoxP3 and Treg deficiency lead to a fatal, T cell dependant, lymphoproliferative immune disorder.
3. Treg in Hematopoietic Stem Cell Transplantation
Tregs prevent GVHD and promote immune reconstitution in HLA-haploidentical transplantation

Di Ianni M et al, Blood, 2011

1. Could Treg infusion prevent GVHD in a setting of haplo-identical HSCT with additional T cells infusion without immunosuppression?

2. Does this strategy could improve immune reconstitution?
Design of the study

• 28 patients, diagnosed with malignancy at very high risk of relapse.
Outcome

• 2/26 patients developed aGVHD (> grade II)
• No patient developed cGVHD. (median follow-up 11.2mo)
• Improved immune reconstitution
Infusion of ex vivo expanded T regulatory cells in adults transplanted with umbilical cord blood: safety profile and detection kinetics.

• 23 patients were evaluated after receiving Treg transfer after double UCB transplant.
• No side effect of Treg transfer
• No increase in infections, risk of relapse
• Lower incidence of grade II-IV aGVHD, no cGVHD in patients receiving high dose Treg

Brunstein CG et al, Blood, 2011
Interleukin-2 and Regulatory T Cells in Graft-versus-Host Disease

Hypothesis: Can low dose of IL-2 expand Treg in vivo and suppress clinical manifestation of steroid refractory chronic GVHD?

Study design:
Patients: 29 enrolled, median age: 49.5, median time since HSCT 1123 days, median time since cGVHD onset 803, median previous therapy for cGVHD: 2, median area of cGVHD: 3 sites.

Time
- Twice daily IL-2 sc during 8 weeks
- Gap of 4 weeks
- Indefinitely IL-2 treatment if clinical benefit
Results I

Safety:
- No patients relapsed or had a progression of cGVHD.
- Side effect most likely due to IL-2 treatment: local induration, systemic symptoms (fever, malaise, fatigue), TTP (including renal failure).

Clinical response: (23 patients evaluated)
- 12 had partial response (>50% improvement).
- 11 had stable disease (<50% improvement or increase <25%) (including 3 with minor objective responses).
- 15 patients received IL-2 for extended period.
Results II

Immunological response:
- Treg expansion up to 8 times the basal level (peak at 4 weeks)
Azacitidine augments expansion of regulatory T cells after allogeneic stem cell transplantation in patients with acute myeloid leukemia (AML)

Goodyear OC et al, Blood, 2012

Aim: To evaluate the safety of AZA administration and immune reconstitution after RIC-HSTC in AML

• 27 patients enrolled
• Median follow-up: 7 months
• AZA treatment started at median time of 64 days. At time of report 16 patients have completed 6 cycles.

Outcome:
• Good tolerance of AZA.
• 3/27 grade II aGVHD, none >grade II aGVHD. 2/27 developed limited cGHVD, non extensive cGVHD.
• 7/27 relapsed.
Results

Treg expansion after RIC-AZA (grey) compared to RIC-controls (black)

Specific tumor antigen response in CD8+ T cells responding to peptides
Treg therapy

Treg modulation during clinical trials in HSCT allows to prevent or improve GVHD outcome.
Regulatory T cells, they do fulfill their promise!
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Thymic Treg development

Josefowicz SZ, Annual Rev Immuno, 2012
Treg as an heterogeneous population

Lei T et al, Bioessays, 2012
Treg prevents acute GVHD without affecting GVT effects in mice

**GROUP 1**
- HSC from haplo-id mice
- Syngeneic tumor cells

**GROUP 2**
- HSC from haplo-id mice
- Syngeneic tumor cells
- Tconv from haplo-id mice

**GROUP 3**
- HSC from haplo-id mice
- Syngeneic tumor cells
- Tconv from haplo-id mice
- Treg from Haplo-id mice

Edinger et al., Nat Med 2003
Treg prevents acute GVHD without affecting GvT effects in mice

Edinger et al., Nat Med 03
APECED (autoimmune polyendocrinopathy, candidiasis, ectodermal dystrophy)

Break in central tolerance. AIRE deficiency. (21q22.3)

Clinical features:
- Autoimmunity: high level of auto-Ab leading to adrenal deficiency, hypothyroiditis, hypoparathyroiditis, diabetes, gonadal failure, GI tract autoimmunity, hepatitis and vitiligo.
- Chronic mucocutaneous candidiasis
- Ectodermal dystrophy

Treg defect: decreased Treg percentage, FoxP3 expression and Treg TCR repertoire diversity.

Treatment: Only supportive

Kekalainen E et al, JI, 2007
Additional PID including Treg defect

- ADA-SCID: altered purine metabolism interferes with normal Treg function.
- Leaky SCID/Omenn Syndrome: low Treg number, oligoclonal TCR repertoire.
- APECED: Lack of Treg TCR repertoire diversity
- ALPS: impaired Treg/effector T cells ratio
- CVID: decrease Treg

Treg as a secondary event in PID

- APECED: Lack of Treg TCR repertoire diversity
- ALPS: impaired Treg/effector T cells ratio
- CVID: decrease Treg