

Induction de tolérance

Bernard Charpentier

CHU Bicêtre

Paris

DST -INDUCED TOLERANCE (1)

K. WOOD

- 1/ PROTOCOL :
 - ANTI CD4 mAb at d-27/-28
 - DST at d-27
- } TRANSPLANTATION d-0
- 2/ LEADS TO INDEFINITE GRAFT PROLONGATION (HEART/MOUSE)
 - 3/ INDUCTION OF Tr, TRANSFERABLE BY 10×10^7 CD4+ → TSP 10 d LATER
 - 4/ MONITORING :
 - PROLIFERATION AGAINST DONOR IDENTICAL vs CONTROLS
 - IL2 AND IFN γ PRODUCTION AGAINST DONOR IDENTICAL vs CONTROLS

MODEL OF COLITIS IN THE MOUSE (2)

K. WOOD

- CD4+ CD45^{HIGH} → COLITIS
 - CD4+ CD45^{LOW} → PROTECTION FROM COLITIS
- } → PROTECTION : ROLE OF IL4-IL10-TGF β ?

DST -INDUCED TOLERANCE (3)

K. WOOD

- **ISOLATION OF CD4+ CD45^{LOW} BY FAX AND MAGNETIC BEADS**
 - **TRANSFERT TOLERANCE**
 - **IS ag SPECIFIC**
 - **NOT PROTECT AGAINST 3rd PARTY**
 - **CD45^{HIGH} RECONSTITUTE REJECTION FROM 3 x 10³ TO 1000 x 10³ CELLS**
 - **NEUTRALISATION OF IL10 (NOT IL4) ABROGATES Tr OF CD45^{LOW}**

IMMUNOSUPPRESSION AFTER NON LYTIC ANTI CD4 mAb TREATMENT IN THE MOUSE (4)

H. WALDMANN

- **PREEXIST**
- **REGULATE BOTH CD4 AND CD8**
- **GENERATED IN PREVIOUSLY IMMUNE ANIMALS**
- **NEED ag TO STAY ACTIVE**
- **COEXISTE WITH ART CELLS**

IMMUNOSUPPRESSION AFTER NON LYTIC ANTI CD4 mAb TREATMENT IN THE MOUSE (3)

H. WALDMANN

A LOT OF MANIPULATION COULD INDUCE THIS STATE

- **ANTI CD4 mAb**
- **BLOCKADE BY CD40-CD40L mAb**
- **DEPLETING ANTI CD3 mAb**
- **INDUCES TOLERANCE TO A 3rd PARTY GRAFT**
- **DEPLETION BY ANTI CD4 mAb INDUCES RUPTURE**

IMMUNOSUPPRESSION AFTER NON LYTIC ANTI CD4 mAb TREATMENT IN THE MOUSE (2)

H. WALDMANN

- **ag SPECIFIC**
- **Tr MUST BE IN THE PERIPHERY**
- **Tr NEED SUSTAINED ag EXPOSURE**
- **TRANSPLANTED TISSUE MAY THE SITE OF Tr**
- **USE OF THE INDIRECT PATHWAY OF ag PRESENTATION**

IMMUNOSUPPRESSION AFTER NON LYTIC ANTI CD4 mAb TREATMENT IN THE MOUSE (1)

H. WALDMANN

- **TRANSFERABLE IS**
- **LINKED TO INFECTIOUS TOLERANCE**
- **DOMINANT TOLERANCE MEDIATED BY CD4+ -T CELLS**
- **IN MANY ORGANS IN NAIVE AND PRIMED RODENTS**

REGULATORY T CELLS (1)

H.D. VOLK

- **MULTI HEART/KIDNEY TRANSPLANTS IN ALLOGENEIC RATS**
 - **AFTER 1 W : REJECTION (100 %)**
 - **AFTER 3 W : TOLERANCE (40 % REJECTION)**
 - **AFTER 6 W : REJECTION (100 %)**
- **UPREGULATION OF Bag-1 (ANTI-APOPTOTIC)**
 - **BINDS TO Bcl2/Bcl x**
 - **PROTECT OF ACTIVATED INDIV. APOPTOSIS**
 - **TREATMENT OF THE 1st GRAFT WITH**
 - **ANTI CD4 mAb**
 - **CTL A4 Ig**

REGULATORY T CELLS (2)

H.D. VOLK

TOLERANCE INDUCED

- IL4/IL10 NOT ESSENTIAL
- Tr : CD4+
- DD-RT-PCR : 75 NOVEL GENES
- THE GRAFT INDUCES ITSELF Tr
- Tr ACCUMULATE IN THE GRAFT
- Tr ARE PROTECTIVE AGAINST AIA (ACTIVATED-INDUCED-APOPTOSIS)

TS LYMPHOCYTES INHIBIT NF-KB MEDIATED TRANSCRIPTION OF CD86 GENE IN APC

LI J. et al., J. Immunol., 1999, 163:6386-6392

