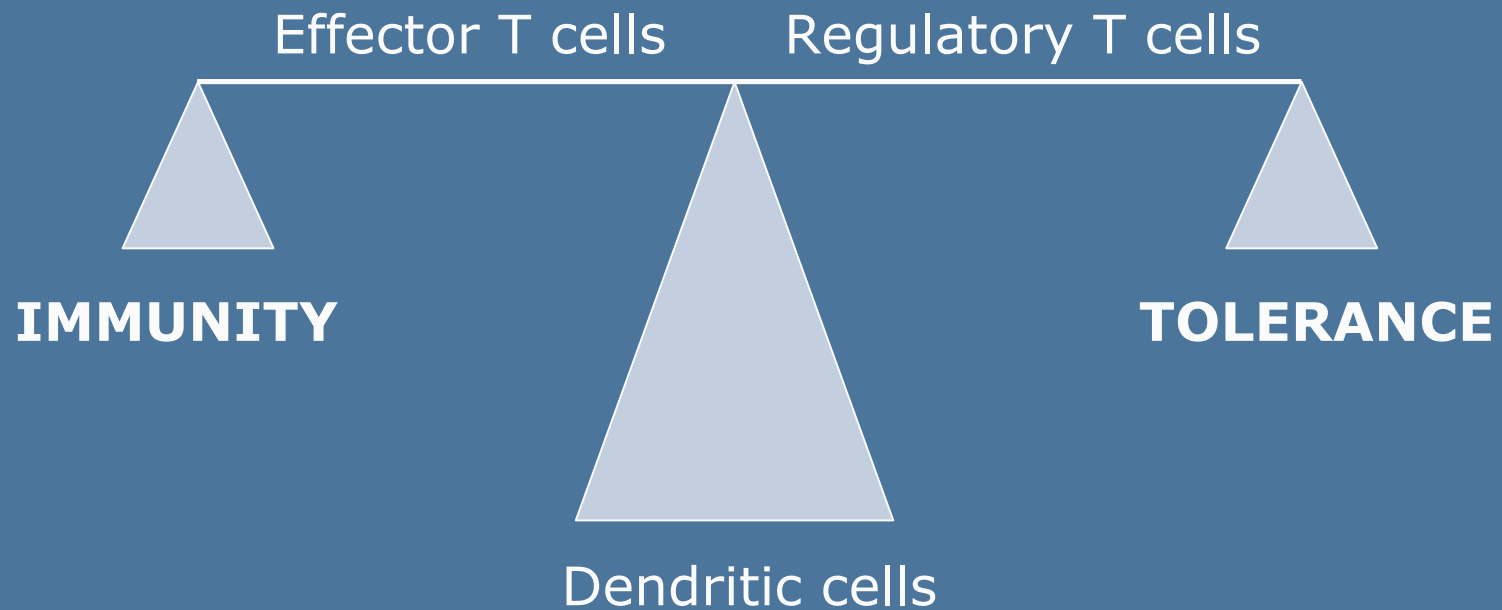


Immunosuppression induced by iDC is mediated by TGF- β and IL-10 double-positive regulatory T cells

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Dendritic cells (DC): key players in tolerance and immunity



Different differentiation stages of DC

- Immature DC
 - High phagocytic activity
 - Low expression of MHC II and costimulatory molecules
 - Limited antigen presenting and migratory function
 - Tolerogenic by induction of regulatory T cells (Treg)
- Mature DC
 - Immunogenic
 - Upregulation of MHC II and costimulatory molecules
 - High antigen presenting function
 - No phagocytic activity
 - HOWEVER: induction of Treg by mature DC

- Objectives

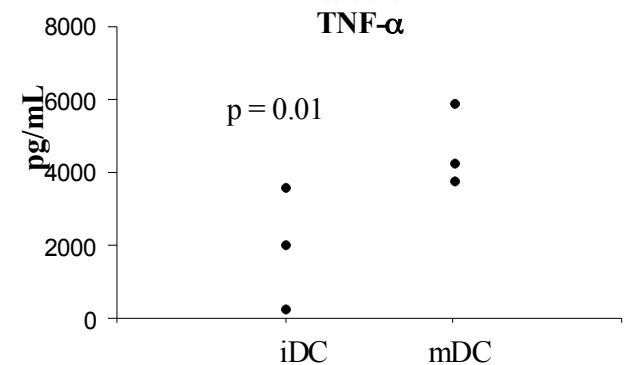
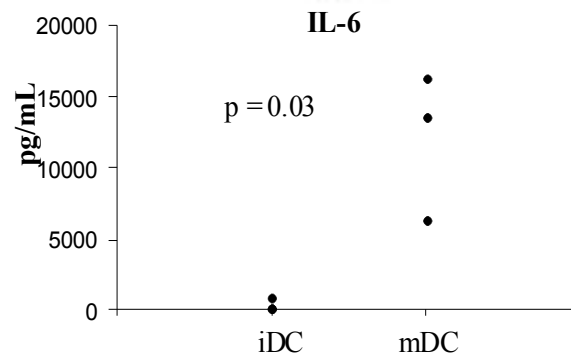
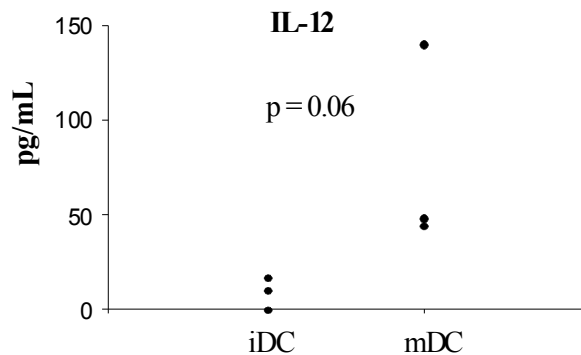
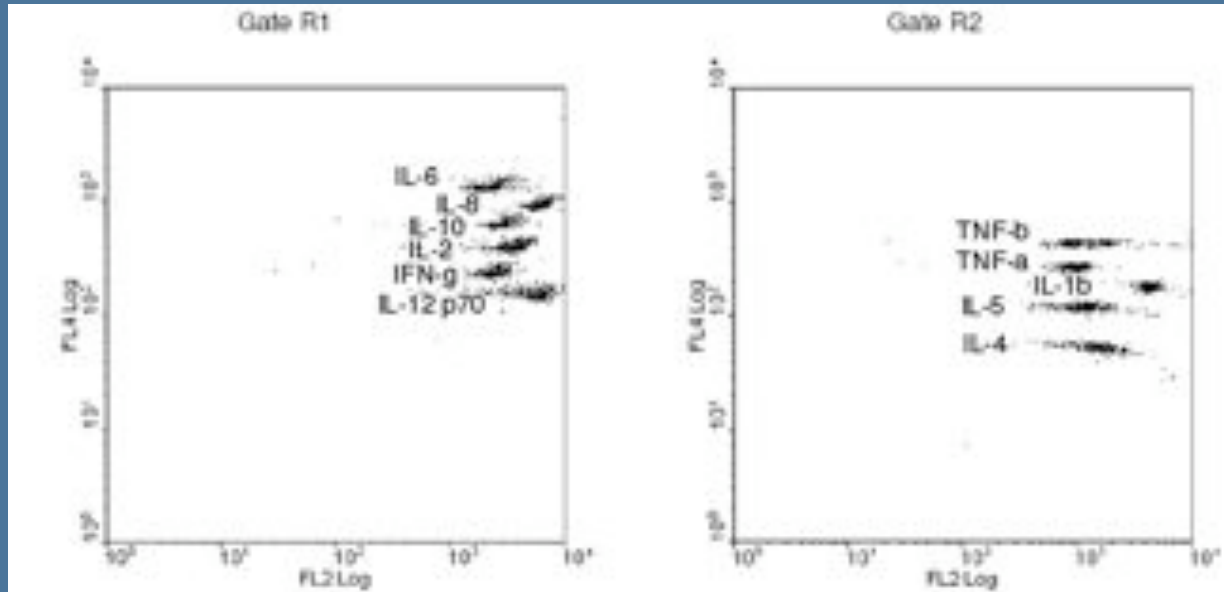
- Antigen presentation by iDC to T cells results in T cell anergy and/or tolerance
 - Absence of inflammatory danger signals in steady-state conditions
 - Low expression levels of costimulatory molecules on iDC
 - Induction of IL-10-producing regulatory T cells

- Aim

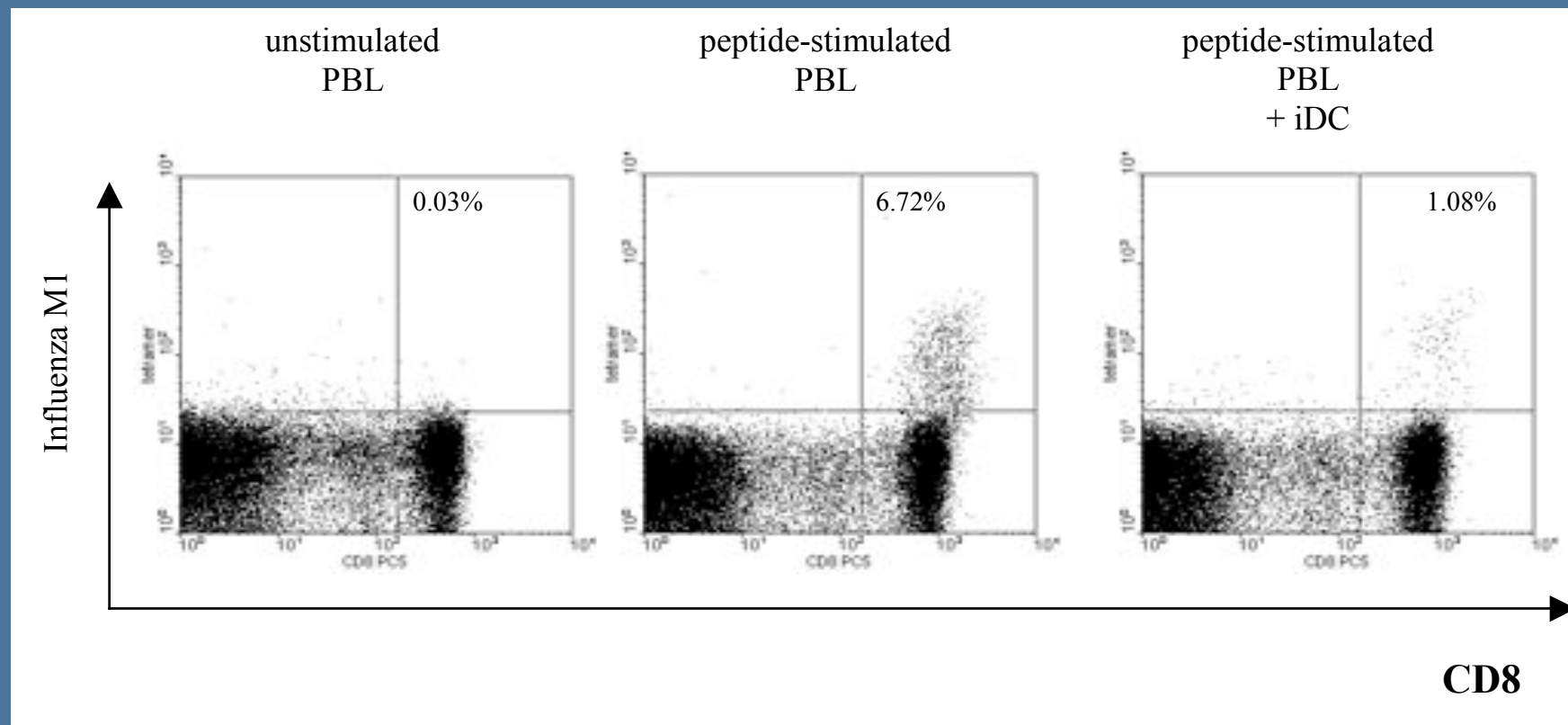
- Investigate the cellular mechanisms of immune suppression induced by iDC

Characterization of monocyte-derived DC

IL-6, TNF- α and IL-12 secretion was significantly increased in supernatant of mDC as compared to that of iDC



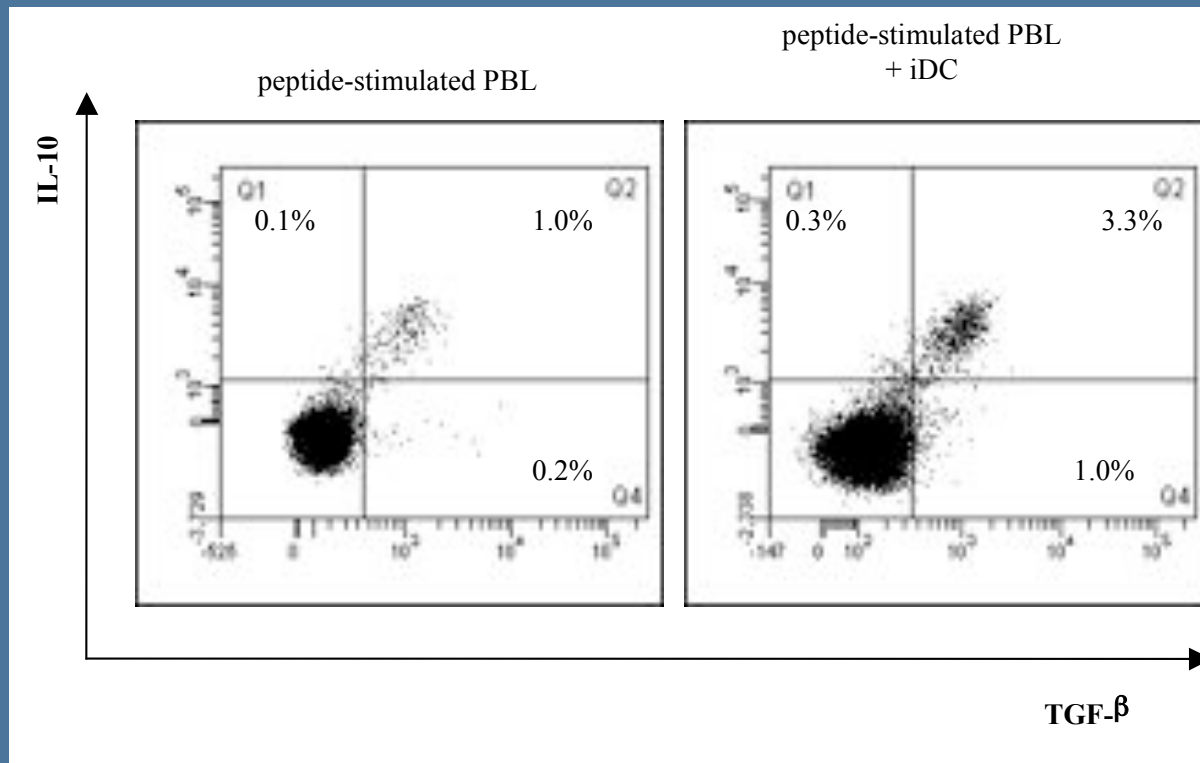
Autologous T cell stimulatory capacity of iDC



Monocyte-derived iDC increase the number of TGF- β and IL-10 double-positive CD4+ T cells (1)

DONOR	% TGF- β + within CD3+CD4+CD25- T cells		% IL-10+ within CD3+CD4+CD25- T cells	
	peptide-stimulated PBL	peptide-stimulated PBL + iDC	peptide-stimulated PBL	peptide-stimulated PBL + iDC
1	0.77	1.28	ND	ND
2	0.44	1.49	ND	ND
3	1.07	3.07	1.25	3.5
4	0.98	2.73	0.94	2.69
Fold increase (mean)		2.68		2.83
p-value		0.015		0.04

Monocyte-derived iDC increase the number of TGF- β and IL-10 double-positive CD4+ T cells (2)

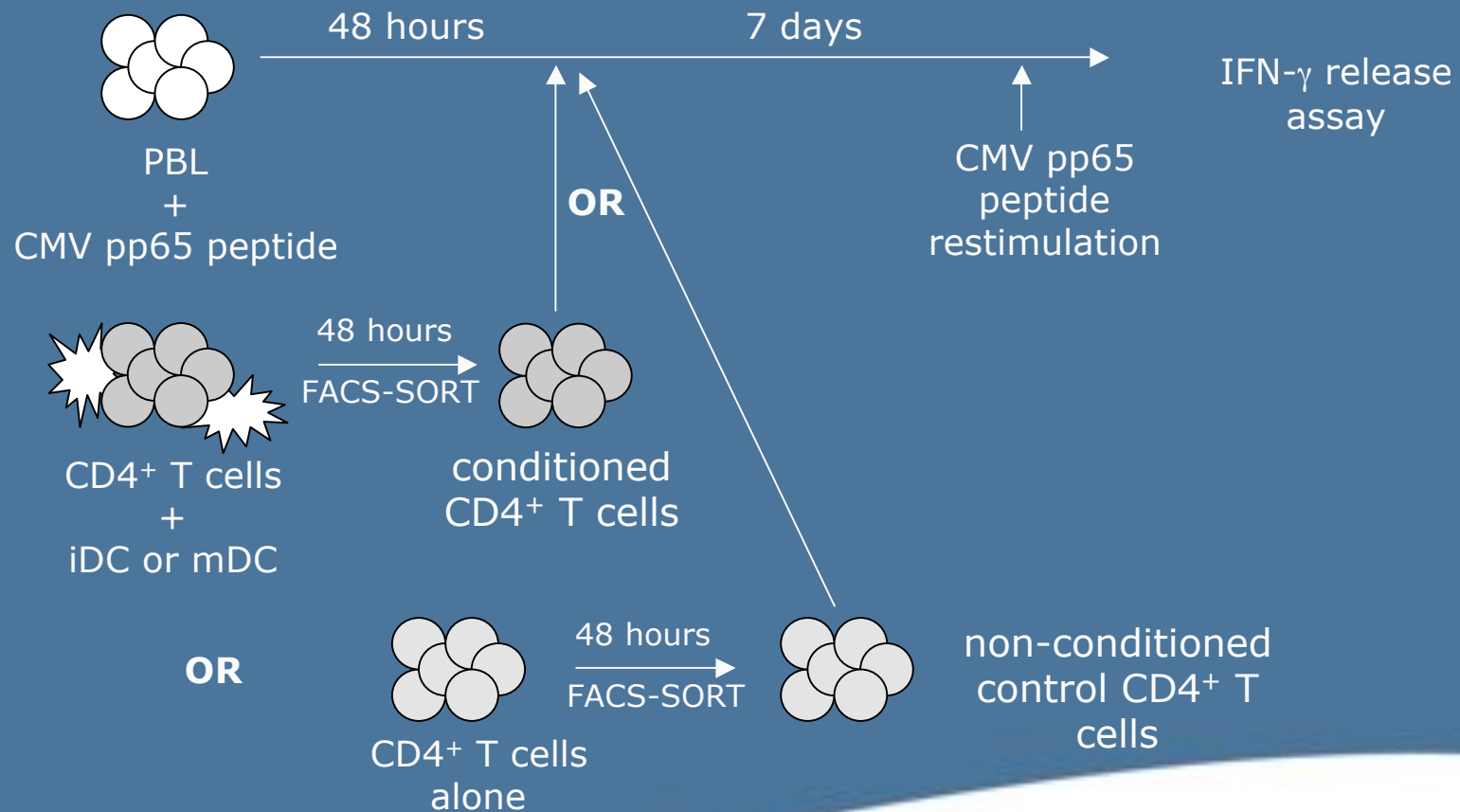


Detailed characterization: CD25-, CD69-, ic CTLA-4- and FOXP3-

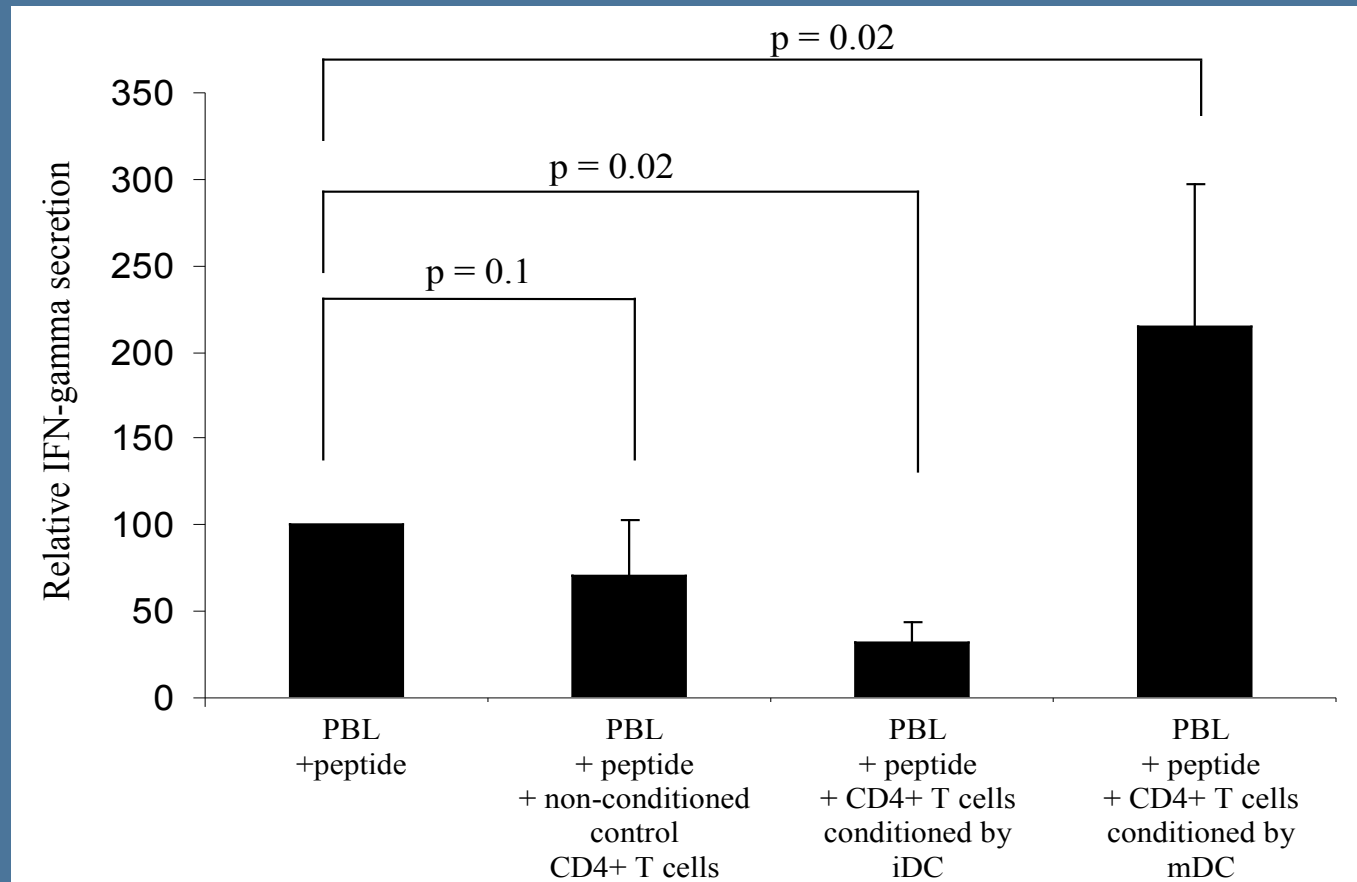
Soluble factors in iDC/T cell coculture supernatant suppress antigen-specific IFN- γ production

	IFN-gamma (pg/mL)			
DONOR	peptide-stimulated PBL + iDC	peptide-stimulated PBL + iDC + anti-TGF- β	peptide-stimulated PBL + iDC + anti-IL-10	peptide-stimulated PBL + iDC + anti-TGF- β + anti-IL-10
1	1 \pm 1	35 \pm 3	62 \pm 18	170 \pm 43
2	156 \pm 28	561 \pm 73	1120 \pm 152	1735 \pm 148
3	790 \pm 224	923 \pm 118	2100 \pm 14	1842 \pm 81
4	350 \pm 94	443 \pm 105	608 \pm 92	1061 \pm 123
p-value ^A		0.07	0.06	0.03

T cell suppression assay



CD4+ T cells conditioned by iDC, but not by mDC, inhibit efficient activation of IFN- γ producing antigen-specific T cells



Conclusion and Perspectives

- DC actively maintain peripheral T cell tolerance
 - induce and/or expand regulatory T cell populations
 - TGF- β /IL-10 double-positive adaptive Treg
 - displayed suppressive activity unless DC were optimally matured
- Future perspective
 - antigen-specific manipulation of auto-immunity
 - expand antigen-specific Treg from polyclonal Treg populations using DC



Thank you...

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