

رویکردی جدید در درمان بیماری دیابت خودایمن وابسته به انسولین با استفاده از سلول‌های دندریتیک تیمار شده با اینترلوکین ۱۰ (IL-10)

*

چکیده

مقدمه:

T

(DCs)

T

IL-4 GM-CSF

LPS IL-10

روش‌ها:

T

IL-10

MHC class II

یافته‌ها:

(P < /)

) LPS

T

IL-10

(P < /)

IFN- γ

IL-10

IL-10

نتیجه‌گیری:

IL-10

واژگان کلیدی:

* نشانی:

moazzeni@dr.com :

تاریخ دریافت مقاله: ۸۴/۷/۲۴

تاریخ پذیرش مقاله: ۸۵/۴/۲۰

مقدمه

(IL-10)

IL-12 IL-10 β T

Th2 IL-10 T

IL-10 T []

T [] T

T [] A []

IL-10 IL-10 []

IL-10 (DC)

IDDM [] T

روش‌ها

C57BL/6 T

(LPS)

% RPMI (Gibco) CpG DNA TNF- α

μ g/ml (Gibco) U/ml FBS (Gibco) CD40 CD40 IFN- γ

(Sigma) (Gibco)

mrTNF- α (Bender mrIL-4(R&D) mrGM-CSF(R&D) []

mrIL-10 (Bender Med) Med T

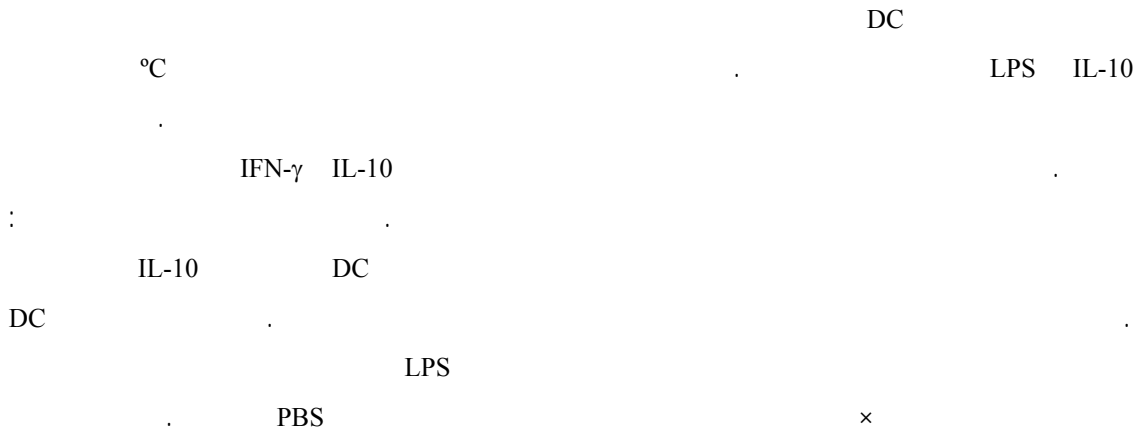
antiCD11c(PE-conjugated) IL-12

anti CD11b(FITC-conjugated) Th2 Th1

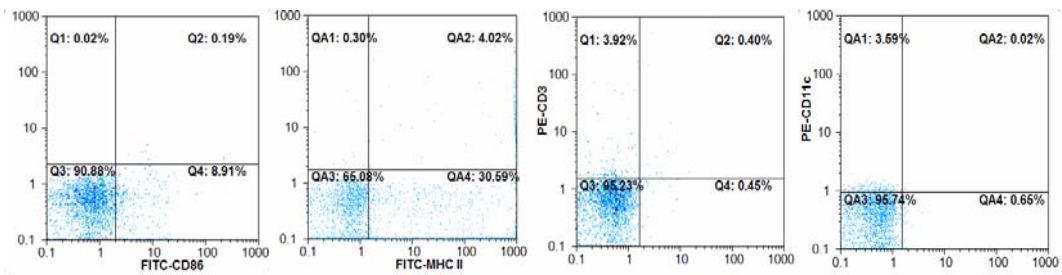
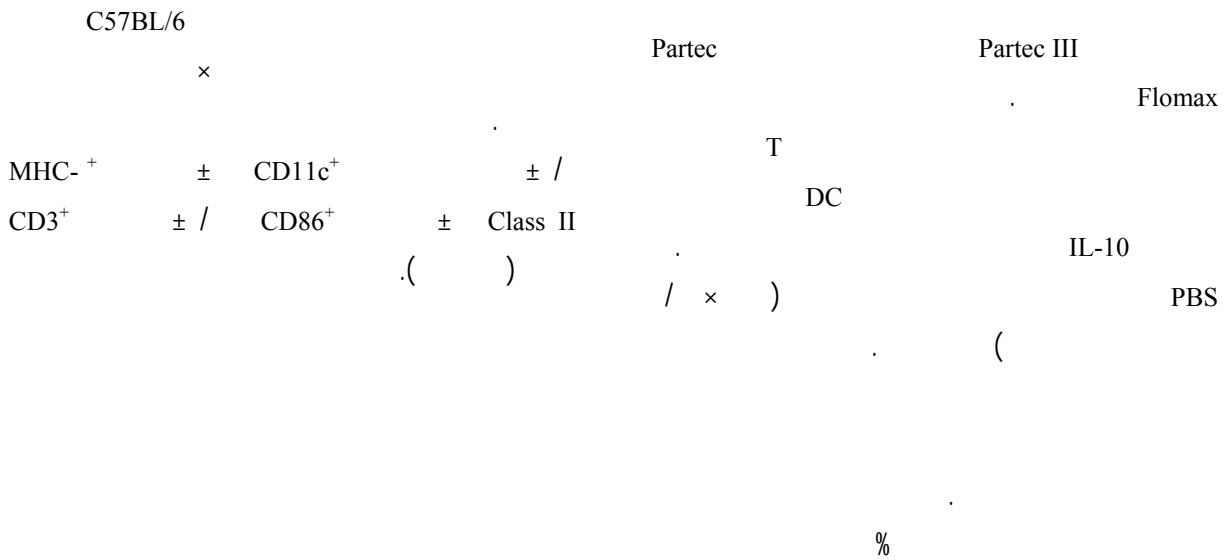
anti CD8 α (PE-conjugated) []

anti-

Haase anti CD40(PE- MHC class II I-A^E(FITC-conjugated)
 U/ml [] anti CD86(PE-conjugated) conjugated)
 anti-CD3(PE-
 % T conjugated)
 IL-10 BD Biosciences
 CO₂ %
 () LPS
 DC
 % /
 g
 % cc
 Polyinosinic-Polycytidylic acid mm PBS
 (poly I/C) cc
 Insulin 2B chain
 peptide B: 9-23(SHLVEALYLVCGERG) / cc
 µg/ml (Flush out)
 g
 DCs)
 T × ()
 DC DC RPMI
 (DC2 DC1)
 MHC-II CD11c DCs U/ml cm²
 CD86 rmIL-4 u/ml rmGM-CSF
 IL-10 % CO₂ °C
 LPS
 CD11b CD8α %
 CD8α
 DC DC
 DC DC
 DC CD11b



یافته ها



نمودار ۱- نمونه ای از نمودارهای حاصل از آنالیز فلوسیتومتری سلولهای بدست آمده از مغز استخوان

% ± MHC ClassII⁺

.% ± CD40⁺ % ± CD86⁺ CD11c⁺ ±

CD86 MHC class II IL-10

LPS) CD11c⁺

(P= /) (

.() MHC % ±

IL-10 . CD40⁺ % ± CD86⁺ % ± ClassII⁺

C11c⁺ CD8α

IL-10 LPS (DC2) CD11b

.()

In vivo

IL-10 Th2

IL-10

In vivo IL-10 LPS

LPS

% ±

T % ±

IL-10 MHC % ± LPS

(SD=) CPM % ± CD86⁺ % ± ClassII⁺

LPS MHC ClassII . CD40⁺

(SD=) CPM

IL-10 MFI

IL-10 (P= /)

T

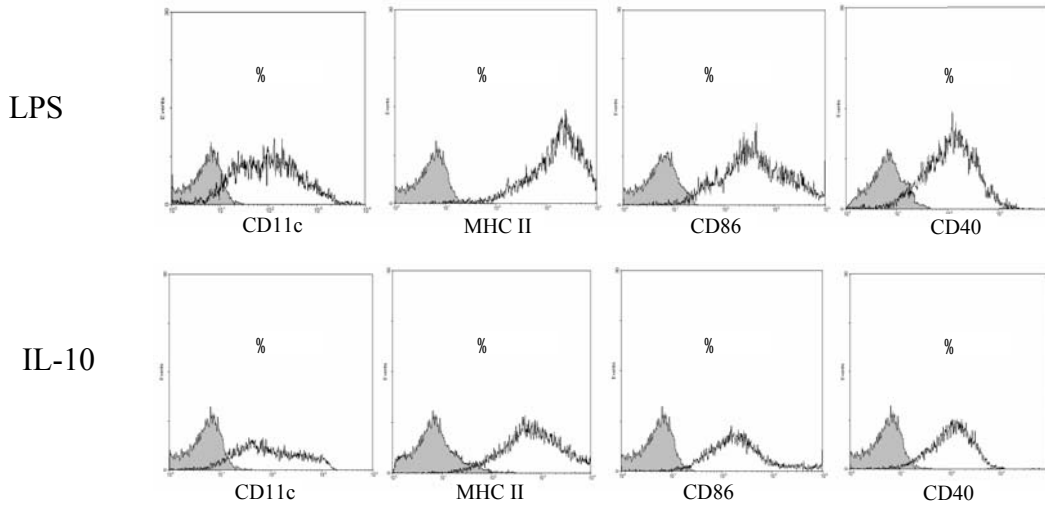
T IL-10 MHC ClassII

.()

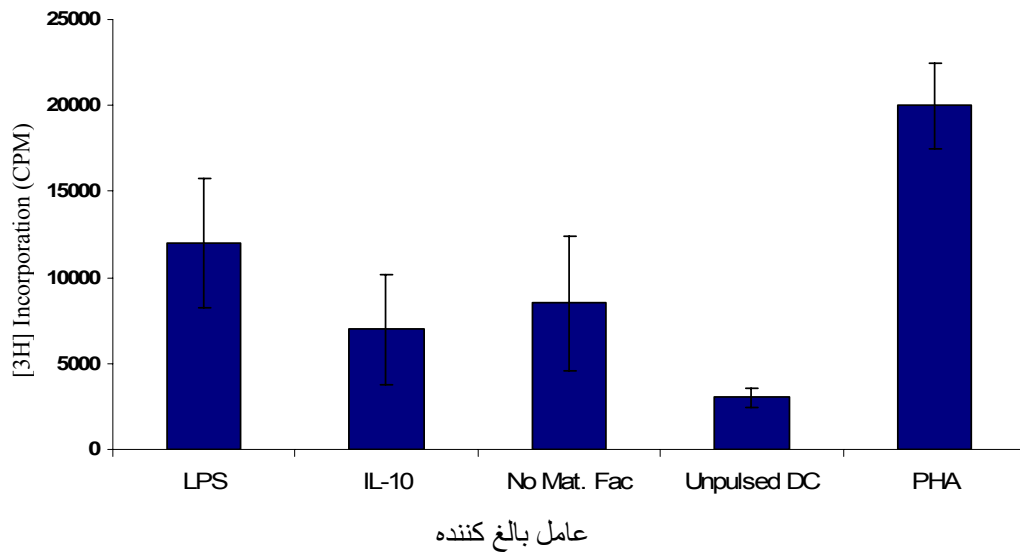
IL-10

.() % ±

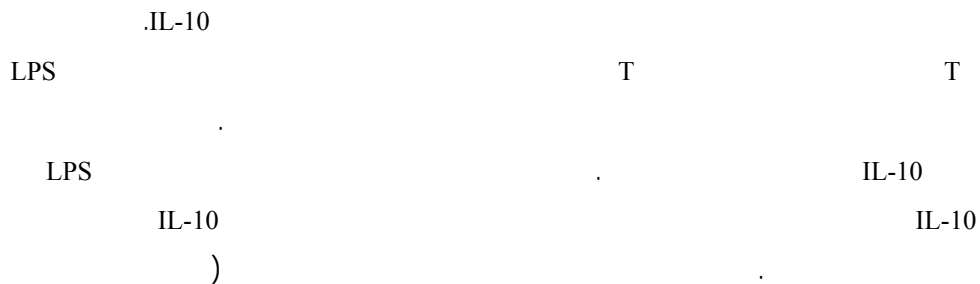
LPS % ±



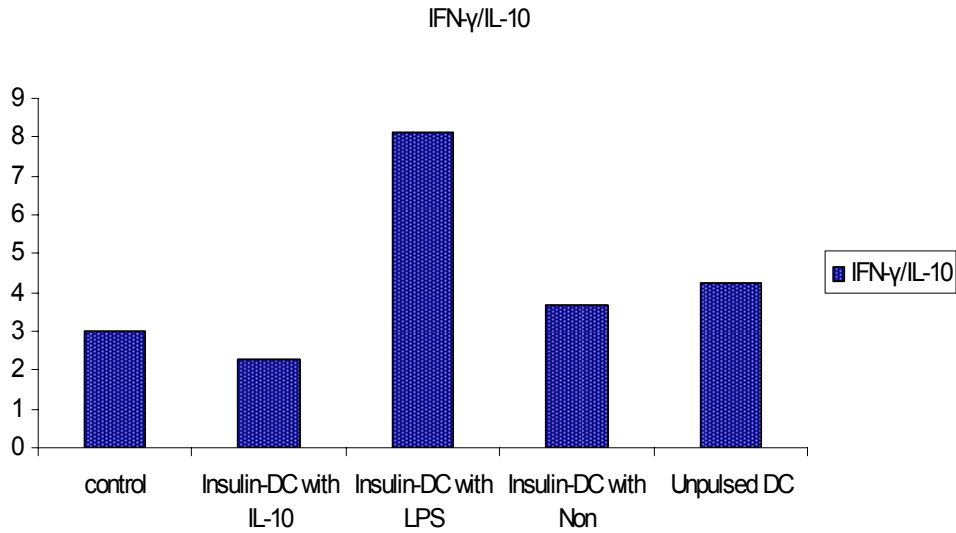
نمودار ۲- میزان بروز هر یک از شاخص‌های بلوغ بر روی سلول‌های دندریتیک بعد از اضافه نمودن عوامل بلوغ. نمودارهای خاکستری مربوط به ایزوتیپ کنترل هر یک از شاخص‌ها بر روی سلول‌های مورد مطالعه می‌باشد.



نمودار ۳- میزان تکثیر سلول‌های T در مواجهه با آنتی‌ژن در آزمون سنجش تکثیر سلول‌های T در گروه‌های مختلف سلول‌های دندریتیک تیمار شده با IL-10 و LPS گروه No Mat. Fac مربوط به سلول‌های دندریتیک است که هیچ عامل بالغ کننده‌ای دریافت نکرده‌اند و unpulsed DC مربوط به گروهی است که با پپتید انسولین بارگذاری نشده‌اند.



IL- Th2 (P < /) IFN-γ/IL-10 (P < /)
 .() LPS
 .()



نمودار ۴- نسبت ساینوکین‌های IFNγ/IL10 تولید شده توسط لنفوسیت‌های T در گروه‌های مورد مطالعه تزریق شده توسط سلول‌های دندریتیکی که به صورت‌های متفاوتی تیمار شده اند.

بحث

GM-CSF + IL-3 + IL- DC
 .[] Th2 T 4 DC T
 DC T DC T
 T IL-10 β₂
 Th2 CD58 CD50, CD54, CD2, β₁
 CD40L IL-12P70 T .[]
 Kalinski.[]
 IL-12 IL-12 IL-1, IL-6
 .[] Th2 Th1 .[]
 IL-10 IFN-γ, PGE₂
 Th2 Th1
 DC
 GM-CSF + IL-3 + IFN-γ
 DC IL-12
 IFN-γ
 Th1 T
 IL-10 .[]
 [] NK

[] Dhodapkar
 IL-10 DC
 . T_{reg} *In vivo*
 IL-10 . []
 T_{reg} T_{reg}
 DC
 . [] T_{reg}
 .
 NOD IL-10
 (CD25⁺CD4⁺) T_{reg}
 [] IL-10 . []
 IL-10
 CD4⁺T
 T *Ex vivo* . []
 DC [] Steinbrink
 T_{reg} GM-CSF IL-4
 IL-10
 DC
 DC CD8⁺T
 Papaccio . IL-10
 HCG
 Th2
 NOD IL-10
 . [] B7-1/-2 MHCII
 IL-10 (ICAM-1)
 DC IL-10 . []
 Th2 T
 IL-1, IL-6, IL-8, TNF- α
 . [] GM-CSF
 BB NOD
 DC
 IL-10 IL-10
 IL-10 [] Th2
In vitro DC
 . []

مآخذ

1. Masteller EL, Bluestone JA. Immunotherapy of insulin-dependent diabetes mellitus. *Curr Opin Immunol* 2002; 14:652-659.
2. Parving H-H, Tarnow L, Nielsen F, Rossing P, Mandrup-Poulsen T, Osterby R, et al. Cyclosporine nephrotoxicity in type 1 diabetic patients. A 7-year follow-up study. *Diabetes Care* 1999; 22: 478-483.
3. Banchereau J, Steinman RM. Dendritic cells and the control of immunity. *Nature* 1998; 392: 245-52.
4. Steinman RM. The dendritic cell system and its role in immunogenicity. *Annu Rev Immunol* 1991; 9: 271-96.
5. Banchereau J, Briere F, Caux C, Davoust J, Lebecque S, Liu YJ, et al. Immunobiology of dendritic cells. *Annu Rev Immunol* 2000; 18: 767-811.
6. Maldonado-Lopez R, De Smedt T, Michel P. CD8alpha+ and CD8alpha- subclasses of dendritic cells direct the development of distinct T helper cells *in vivo*. *J Exp Med* 1999; 189:587-92.
7. Constant S, Pfeiffer C, Woodard A, Pasqualini T, Bottomly K. Extent of T cell receptor ligation can determine the functional differentiation of naive CD4+ T cells. *J Exp Med* 1995; 182:1591-6.
8. Hosken NA, Shibuya K, Heath AW, Murphy KM, O'Garra A. The effect of antigen dose on CD4+ T helper cell phenotype development in a T cell receptor-alpha beta-transgenic model. *J Exp Med* 1995; 182: 1579-84.
9. Freeman GJ, Boussiotis VA, Anumanthan A. B7-1 and B7-2 do not deliver identical costimulatory signals, since B7-2 but not B7-1 preferentially costimulates the initial production of IL-4. *Immunity* 1995; 2: 523-32.
10. Jonuleit H, Schmitt E, Schuler G, Knop J, Enk AH. Induction of interleukin 10-producing, nonproliferating CD4+ T cells with regulatory properties by repetitive stimulation with allogeneic immature human dendritic cells. *J Exp Med* 2000; 192: 1213-22.
11. Koch F, Stanzl V, Jennewein P, Janke K, Heuffler C, Kaempgen E, et al. High level IL-12 production by murine dendritic cells: upregulation via MHC class II and CD40 molecules and downregulation by IL-4 and IL-10. *J Exp Med* 1996; 184: 741-6.
12. Huang LY, Sousa CR, Itoh Y, Inman J, Scott DE. IL-12 induction by a Th1 inducing adjuvant *in vivo*: dendritic cell subsets and regulation by IL-10. *J Immunol* 2001; 167: 1423-30.
13. De Smedt T, Van Mechelen M, De Becker G, Urbain J, Leo O, Moser M. Effect of interleukin -10 on dendritic cell maturation and function. *Eur J Immunol* 1997; 27: 1229-35.
14. Faulkner L, Buchan G, Baird M. Interleukin-10 does not affect phagocytosis of particulate antigen by bone marrow-derived dendritic cells but does impair antigen presentation. *Immunology* 2000; 99: 523-31.
15. Buelens C, Willems F, Delvaux A, Pierard G, Delville JP, Velu T, Goldman M. Interleukin-10 differentially regulates B7-1 (CD80) and B7-2 (CD86) expression on human peripheral blood dendritic cells. *Eur J Immunol* 1995; 25: 2668-72.
16. Steinbrink K, Wolf M, Jonuleit H, Knop J, Enk AH. Induction of tolerance by IL-10 treated dendritic cells. *J Immunol* 1997; 159: 4772-80.
17. Morel AS, Quarantino S, Douek DC, Londei M. Split activity of interleukin-10 on antigen capture and antigen presentation by human dendritic cells: definition of a maturative step. *Eur J Immunol* 1997; 27: 26-34.
18. Rieser C, Ramoner R, Bock G, Deo YM, Holtl L, Bartsch G, Thurnher M. Human monocyte-derived dendritic cells produce macrophage colony-stimulating factor: enhancement of c-fms expression by interleukin-10. *Eur J Immunol* 1998; 28: 2283-8.
19. Allavena P, Piemonti L, Longoni D, Bernasconi S, Stoppacciaro A, Ruco L, Mantovani A. IL-10 prevents the differentiation of monocytes to dendritic cells but promotes their maturation to macrophages. *Eur J Immunol* 1998; 28: 359-69.
20. Haase C, Jorgensen TN, Michelsen BK: Both exogenous and endogenous interleukin-10 affects the maturation of bone-marrow-derived dendritic cells *in vitro* and strongly influence T-cell priming *in vivo*. *Immunology*. 2002; 107: 489-99.
21. Hart, D.N: Dendritic cells: unique leukocyte populations which control the primary immune response. *Blood* 1997; 90: 3245-87.
22. Bell, D., Young, J.W., Banchereau, J: Dendritic cells. *Adv Immunol* 1999; 72: 255-324.
23. Ni, K., O'Neill, H.C: The role of dendritic cells in T cell activation. *Immunol Cell Biol* 1997; 75: 223-230.
24. Sato, M., Iwakabe, K., Kimura, S., Nishimura, T: Functional skewing of bone marrow-derived dendritic cells by Th1- or Th2- inducing cytokines. *Immunol Lett* 1999; 67: 63-8.
25. Liu, L., Rich, B.E., Inobe, J., Chen, W., Weiner, H.L. Induction of Th2 cell differentiation in the primary immune response: dendritic cells isolated from adherent cell culture treated with IL-10 prime naive CD41 T cells to secrete IL-4. *Int Immunol* 1998; 10: 1017-26.

26. Kalinski, P.K., Hilkens, C.M.U., Wierenga, E.A., Kapsenberg, M.L. T-cell priming by type-1 and type-2 polarized dendritic cells: the concept of a third signal. *Immunol Today* 1999; 20: 561-7.
27. Mocellin S, Panelli MC, Wang E, Nagorsen D, Marincola FM. The dual role of IL-10. *Trends Immunol* 2003; 24: 36-43.
28. Gerosa F, Baldani-Guerra B, Nisii C, Marchesini V, Carra G, Trinchieri G. Reciprocal activeeeting interaction between natural killer cells and dendritic cells. *J Exp Med* 2002; 195: 327-33.
29. Janjic BM, Lu G, Pimenov A, Whiteside TL, Storkus WJ, Vujanovic NL. Innate direct anticancer effector functions of human immature dendritic cells. I. Involvement of an apoptosis-inducing pathway. *J Immunol* 2002; 168: 1823-30.
30. Albert ML, Sauter B, Bhardwaj N. Dendritic cells acquire antigen from apoptotic cells and induce class I-restricted CTLs. *Nature* 1998; 392: 86-9.
31. Ignatius R, Marovich M, Mehlhop E, Villamide L, Mahnke K, Cox WI, et al. Canarypox virus-induced maturation of dendritic cells is mediated by apoptotic cell death and tumor necrosis factor a secretion. *J Virol* 2000; 74: 11329-38.
32. Moore KW, de Waal Malefyt R, Coffman RL, O'Garra A. Interleukin-10 and the interleukin-10 receptor. *Annu Rev Immunol* 2001; 19: 683-765.
33. Cavaillon, J.M. Pro-versus anti-inflammatory cytokines: myth or reality. *Cell Mol Biol (Noisy-le-grand)* 2001; 47: 695-702.
34. Steinbrink K, Jonuleit H, Muller G, Schuler G, Knop J, Enk AH. Interleukin-10-treated human dendritic cells induce a melanoma antigen-specific anergy in CD8+ T cells resulting in a failure to lyse tumor cells. *Blood* 1999; 93: 1634-42.
35. de Waal Malefyt RW, Yssel H, Roncarolo MG, Spits H, de Fries JE. Interleukin-10. *Curr Opin Immunol* 1992; 4: 314-20.
36. Hsu DH, Oore KW, Spits H. Differential effects of interleukin-4 and -10 on interleukin-2-induced interferon-g synthesis and lymphokine- activated killer activity. *Int Immunol* 1992; 4: 563-9.
37. de Waal Malefyt RW, Haanen J, Spits H, Roncarolo MG, te Velde A, Figdor C, Johnson K, Kastelein R, Yssel H, de Vries JE: Interleukin-10 (IL-10) and viral IL-10 strongly reduce antigen-specific human T cell proliferation by diminishing the antigen-capacity of monocytes via downregulation of class II major histocompatibility complex expression. *J Exp Med* 1991; 174: 915-24.
38. Fiorentino DF, Zlotnik A, Vieira P, Mosmann TR, Howard M, Moore KW, O'Garra A. IL-10 acts on the antigen-presenting cell to inhibit cytokine production by Th1 cells. *J Immunol* 1991; 146: 3444-51.
39. Bogdan C, Nathan C. Modulation of macrophage function by transforming growth factor beta, interleukin-4, and interleukin-10. *Ann N Y Acad Sci* 1993; 685: 713-39.
40. De Smedt T, Van Mechelen M, De Becker G, Urbain J, Leo O, Moser M. Effect of interleukin-10 on dendritic-cell maturation and function. *Eur J Immunol* 1997; 27: 1229-35.
41. Huang L Y, Sousa CR, Itoh Y, Inman J, Scott DE. IL-12 induction by a Th 1-inducing adjuvant in vivo: dendritic cell subsets and regulation by IL-10. *J Immunol* 2001; 167: 1423-30.
42. Dhodapkar MV, Steinman RM, Krasovsky J, Munz C, Bhardwaj N. Antigen-specific inhibition of effector T cell function in humans after injection of immature dendritic cells. *J Exp Med.* 2001; 193: 233-8.
43. Groux H, O'Garra A, Bigler M, Rouleau M, Antonenko S, De Vries JE, Roncarolo NG. A CD4+ T-cell subset inhibits antigen-specific T-cell responses and prevents colitis. *Nature* 1997; 389: 737-42.
44. Asseman C, Mauze S, Leach MW, Coffman RL, Pwrie F. An essential role for interleukin-10 in the function of regulatory T cells that inhibit intestinal inflammation. *J Exp Med* 1999; 190: 995-1004.
45. McHugh, R.S., and E.M. Shevach. Cutting edge: depletion of CD4+CD25+ regulatory T cells is necessary, but not sufficient, for induction of organ-specific autoimmune disease. *J Immunol* 2002; 168 :5979-5983.
46. Tarbell KV, Yamazaki S, Olson K, Toy P, Steinman RM. CD25+ CD4+T Cells, Expanded with Dendritic Cells Presenting a Single Autoantigenic Peptide, Suppress Autoimmune Diabetes. *J Exp Med.* 2004 199:1467-1477.
47. Papaccio G, Nicoletti F, Aurelio F, Bendtzen K, Galdieri M. Prevention of Spontaneous Autoimmune Diabetes in NOD Mice by Transferring In Vitro Antigen-Pulsed Syngeneic Dendritic Cells. *Endocrinology* 2000; 141: 1500-1505.