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Dendritic cells in tolerance and autoimmune diabetes

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Type 1 diabetes is a T cell mediated autoimmune disease where both central and peripheral mechanisms effect T cell tolerance induction. Dendritic cells (DCs) are key regulators of innate and adaptive immune responses. They significantly contribute to central and peripheral T cell tolerance and, following maturation, induce the activation and differentiation of naïve T cells into effector and memory cells. DCs are also major actors in inflammation. Given these multiple effects on immune responses, DCs are suspected to contribute to autoimmune diseases. In this review we discuss how some specific features of DC may contribute to type 1 diabetes.

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Introduction

Dendritic cells (DCs) constitute a heterogeneous collection of professional antigen presenting cells (APC) with different phenotype, tissue localization and function [1,2]. Each DC subset derives from a common myeloid precursor. Plasmacytoid DC (pDC) differentiate in the bone marrow (BM) and immature pDC access lymphoid organs and, under some restricted inflammatory conditions non-lymphoid tissues, through the blood circulation. Conventional DC (cDC) are the second heterogeneous population of DC found in lymphoid organs and non-lymphoid tissues. Unlike pDC, cDC derive from a common pre-DC precursor that differentiates in lymphoid and non-lymphoid tissues. Two major cDC subsets are found in lymphoid organs, namely the CD8 α ⁺Sirp α [−]CD11b[−] and CD8 α [−]Sirp α ⁺CD11b⁺ cDC, referred to thereafter as CD8⁺ and Sirp α ⁺ DC respectively. These two subsets are also found in non-lymphoid

tissues but express a different phenotype. In peripheral tissues, CD103⁺CD11b[−] and CD103[−]CD11b⁺ cDC are the counterparts of the lymphoid CD8⁺ and Sirp α ⁺ DC subsets, respectively. The CD103[−]CD11b⁺ subset, however, also includes monocyte-derived DC in lymphoid and non-lymphoid tissues.

cDC have a unique capacity for CD4 and CD8T cell priming and CD8⁺DC are exquisitely efficient at cross-presenting exogenous antigen to CD8T cells [1–3]. pDC, on the other hand, are characterized by their rapid and massive production of type I interferon (IFN) in response to TLR7/9 engagement with nucleic acids [4]. Although, they present antigen to both CD4 and CD8T cells, pDC are not essential for the initiation of most immune responses. cDC and pDC contribute to central and peripheral T cell tolerance (see below).

Thymic dendritic cells and central tolerance

In contrast to the DCs found in other lymphoid organs, thymic DC (tDC) possess high antigen-presenting capacities and are able to cross present antigens to CD8T cells in the absence of danger or inflammatory signals [3]. These features likely allow for optimal self-antigen presentation and therefore tolerance induction.

The relative contribution of the different tDC subsets to central tolerance *in vivo* is still poorly understood. However, substantial evidence indicates that tDCs contribute to CD4 and CD8T cell deletion as well as to natural regulatory T cells (nTreg) generation *in vivo*.

Thymic DC are found in close interaction with medullary thymic epithelial cells (mTEC), a strategic localization that may optimize the uptake of peripheral tissue specific antigens (TSA) expressed by mTEC [5]. Indeed, among the different stromal and hematopoietic cells of the thymus, only tDC are able to present TSA to CD4T cells *in vitro* [6]. In transgenic mice expressing the model protein antigen ovalbumin (OVA) under the rat insulin promoter leading to ectopic expression of OVA in mTEC, the deletion of OVA-specific CD4T cells was mediated by tDC exclusively while both mTEC and tDC induced deletion of CD8T cells [7]. Similarly, in transgenic mice with *Aire* promoter-driven expression of model protein antigens selectively in mTEC, tDC were found to contribute to CD4T cell deletional tolerance [8–10]. Interestingly, in these experimental models mTEC mainly induced the development of nTreg [8,9]. Although several additional studies highlighted the role of mTEC in

2 Autoimmunity

inducing nTreg cell development, tDC are likewise efficient nTreg inducers [11–13].

Induction of central tolerance by peripheral DC

Thymic CD8⁺ DC derive from BM-precursors that differentiate locally [14]. In agreement with their BM developmental pathway, thymic pDC are mainly of peripheral origin. Recent studies showed that about 30% of thymic Sirpα⁺ DC correspond to peripheral Sirpα⁺ cDC homing to the thymus [15[•]]. Quite remarkably, both peripheral immature Sirpα⁺ cDC and pDC were shown to transport antigen deposited in the skin to the thymus [16[•],17[•],18[•]].

Homing of peripheral DC to the thymus was therefore proposed as an additional mechanism of central tolerance to peripheral tissue antigen. This mechanism may not only extend the pool of self-antigens presented locally for central tolerance but may also integrate the antigenic diversity generated by post-translational modifications that may occur in different tissues (see below). Whether this mechanism actually contributes to central tolerance remains an open question.

Migratory DC found in non-lymphoid tissues continuously traffic to draining LN through afferent lymphatics under steady state conditions, thereby contributing to peripheral self-tolerance. Most DC remain and die within draining LN but a minute fraction, estimated at around 20 000 DC/day, can reach the efferent lymphatics and subsequently the blood circulation [19]. Only 0.2% of circulating DC, corresponding therefore to 40–80 cells/day, may home to the thymus [15[•]]. Among those, only a few may present peripheral tissue antigens under steady-state conditions. In one study peripheral DC were shown to tolerize CD4T cells specific for an antigen expressed in the heart, although expression of the antigen by mTEC was not formally excluded [16[•]]. Older studies however showed that circulating steady state DC do not induce central CD8T cell tolerance in transgenic mice expressing OVA in the pancreas [20]. Additional studies are therefore clearly required to clarify the relative contribution of recirculating peripheral DC in central tolerance.

Thymus Specific Serine Protease and central tolerance

Given the major role of mTEC and tDC at inducing central tolerance, the antigen presenting machinery of both cell types was expected to mirror that of peripheral DC [21]. We found however that all tDC subpopulations, as well as the cTEC but not the mTEC, express the Thymus Specific Serine Protease (TSSP) while it is barely detectable in peripheral DC [22^{••}], K Mahiddine, unpublished observation). In Human, *prss16*, the gene coding for TSSP, is associated with a diabetes susceptibility locus [23]. However, no functional polymorphisms

were detected in *prss16* and TSSP is similarly expressed in diabetes-resistant or susceptible mice strains ([24,25] and K Mahiddine, unpublished observation). Remarkably, we found that TSSP-deficient NOD mice are completely protected from spontaneous type 1 diabetes and severe insulinitis [22^{••}]. We further showed that diabetes resistance was a unique property of the CD4T cell compartment without global alteration of the Treg compartment. Extensive analysis of the intra-thymic development of several islet-specific CD4T cells showed that TSSP-deficiency leads to the deletion of a substantial number of those CD4T cells by BM-derived APC. Hence, although TSSP-deficient NOD mice maintained InsB9-23-specific and GAD-specific CD4T cells, around 40% of the tested specificities were not selected in these mice, including CD4T cells expressing the highly diabetogenic NY4.1 CD4T cell receptor ([22^{••}] and unpublished observation).

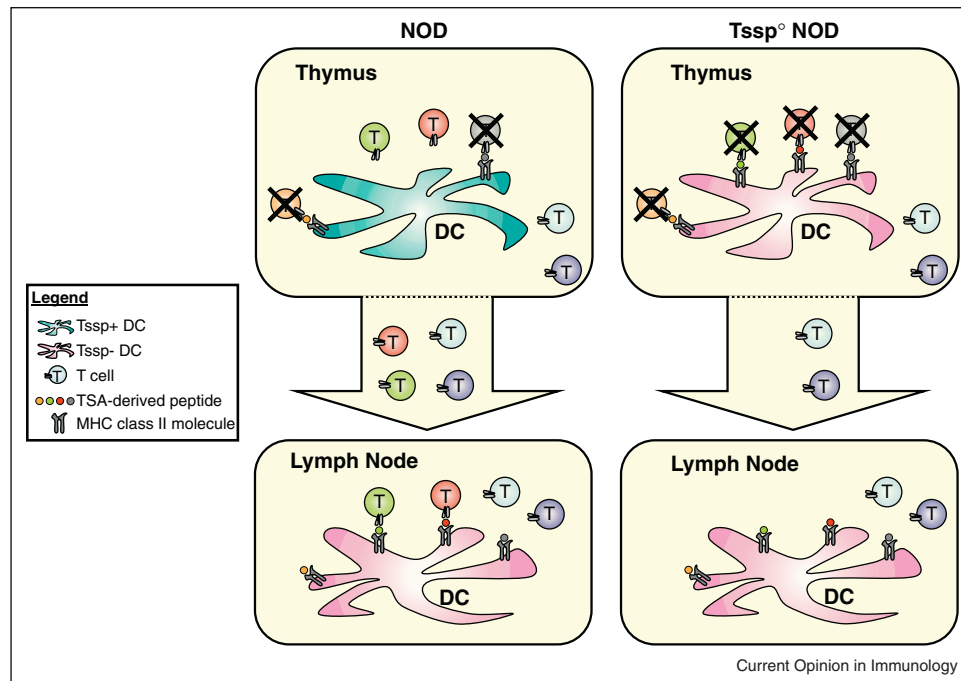
Our results suggest that TSSP, by yet unknown mechanisms, impairs the presentation by tDC of some TSA and consequently limits CD4T cell tolerance (Figure 1). The extent to which TSSP effects central tolerance may vary with the mouse genetic background. Indeed NOD thymocytes are exquisitely resistant to TCR induced apoptosis [26–28]; any mechanism that may reduce antigen presentation, as is the case for TSSP in tDC, may therefore significantly affect deletional tolerance. Such effects may be milder in other strains of mice, an issue that remains to be addressed.

Tissue specific antigen presentation may generate neo-self antigens

There is a strong association between particular MHC class II molecules and type 1 diabetes in both humans and mice. Diabetes susceptibility class II alleles in mice and humans present an amino acid substitution in the peptide binding groove that may affect not only the stability of MHC class II peptide complexes but also the diversity and register of peptide binding [29–31,32^{••},33^{••}].

CD4T cell responses to the InsB9-23 peptide are thought of as a major driver of diabetes [34]. Two types of CD4T cells specific for the InsB9-23 peptide have been generated and both induce diabetes when transferred into NOD mice. Unexpectedly, while both efficiently responded to the InsB9-23 peptide, only type A but not type B T cells responded to the insulin protein when presented by spleen APC. However both type A and type B T cells reacted with unpulsed islet DC or with spleen DC incubated with beta-cell granules. Additional studies suggest that the InsB9-23 peptide binds to IAg7 class II molecules in two different registers [30^{••},31^{••},32^{••}]. The register recognized by type B T cells was only generated when DC were confronted with insulin in the islets, suggesting possible local processing events and/or high local concentration of insulin. Chromogranin A is another

Figure 1



TSSP is a critical regulator of type 1 diabetes. TSSP is expressed by all thymic but not by peripheral DC. TSSP, by yet unknown mechanisms, impairs the presentation by tDC of some class II binding ligands derived from islet-specific antigens (left panel). Consequently in WT NOD mice autoreactive CD4T cells gain access to the periphery. Since peripheral DC do not express TSSP, even in WT NOD mice, they may present these islet-antigens and therefore stimulate the autoreactive CD4T cells that have escape central tolerance. Those diabetogenic CD4T cells are deleted in TSSP-deficient mice (right panel). Consequently, WT but not TSSP-deficient NOD mice develop diabetes.

islet antigen targeted by highly diabetogenic BDC-2.5 and BDC-10.1 CD4T cells [33^{••}]. These TCRs react with the WE14 peptide from chromogranin A, a naturally occurring hormone generated by beta cells. While APC isolated from islets efficiently stimulate the two CD4T cells, high peptide concentrations were required to stimulate these cells. Treatment of the WE14 peptide with the enzyme transglutaminase generated a highly immunogenic peptide, suggesting that post-translational modification may occur in the islets [35^{••}].

Dendritic cells in the islet of Langerhans

Like most peripheral tissues, islets of Langerhans contain DC that are in close proximity with intra-islet blood vessels [36,37]. In NOD mice, islets mainly contain the two major subsets of migratory cDC, the CD103⁺CD11b⁻ and CD103⁻CD11b⁺ subsets [37,38]. Both subsets express high MHC class II levels but low levels of CD80/CD86 and CD40 costimulatory molecules, which reflect a semi-mature phenotype [37,38]. A similar number, frequency and phenotype of these DC subsets are found in pre-diabetic 4–5-week old NOD mice or in NOD-RAG^{-/-} and B6 mice indicating that diabetes susceptibility is not linked to alteration in the cDC composition of islets. However, unlike non-autoimmune

mice strains, NOD mice showed a progressive infiltration of pDC within the islets [39,40^{••}].

At steady state, DC in pancreatic LN present islet-derived antigens to CD4T cells and CD8T cells [36,37]. The islets of Langerhans, therefore, like other tissues, contain different subsets of DC that migrate to draining LN and present antigens to either CD4 or CD8T cells. These events generally contribute to peripheral T cell tolerance (reviewed in [41]). In the NOD mice, however, such presentation may promote autoimmune diabetes [42].

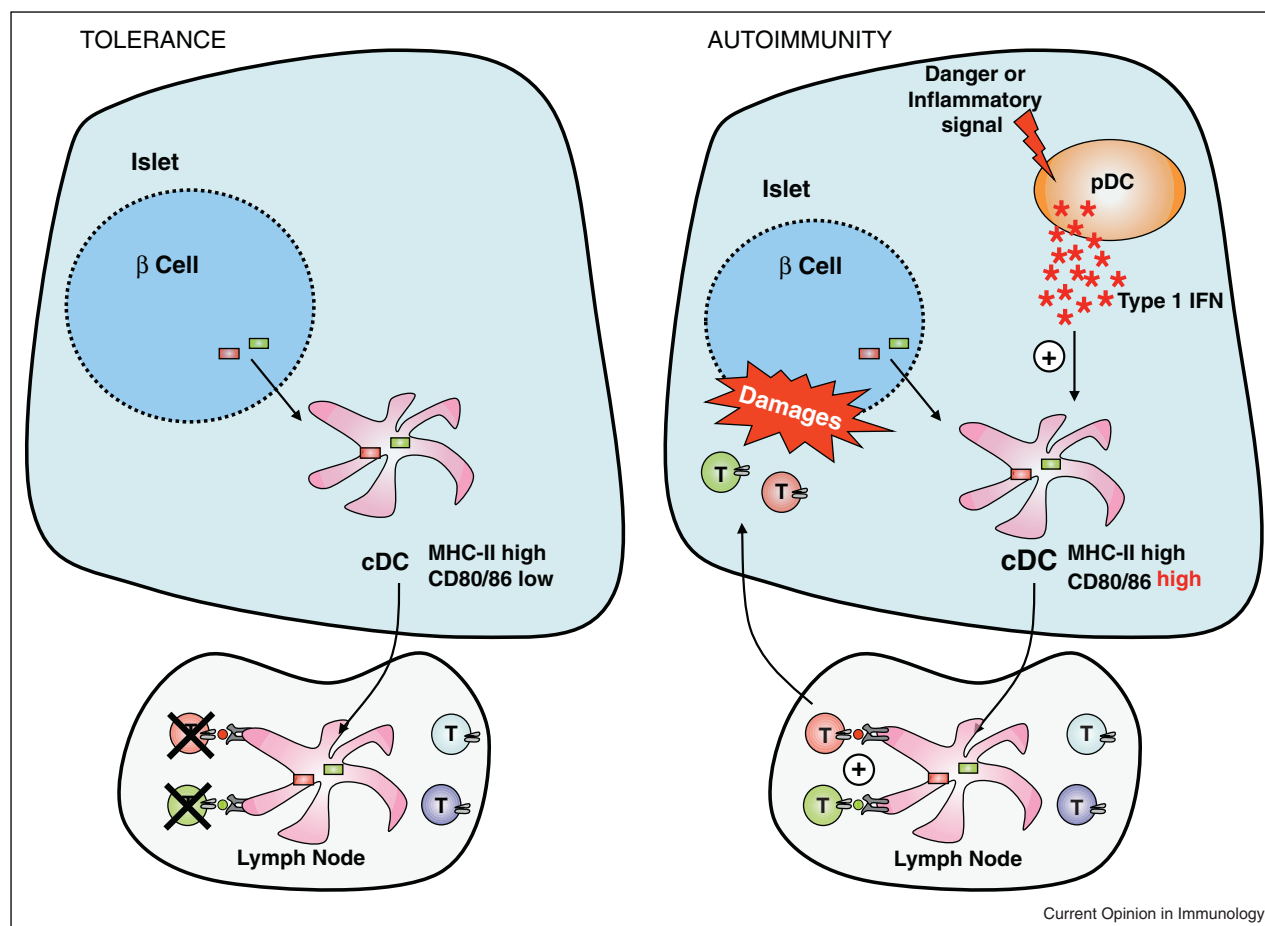
Dendritic cells in the development of autoimmune diabetes

While immature steady state DC are globally tolerogenic, mature DC drive T cell activation and effector T cell differentiation due to enhanced expression of costimulatory molecules and polarizing cytokines. Danger and inflammatory signals will induce DC maturation.

Toll like receptors (TLR) can sense dead cells or self-DNA that is released in the extracellular milieu when clearance of apoptotic cells is impaired. The observation that Myd88-deficient NOD mice are resistant to diabetes suggests that TLR and/or other Myd88-dependent

4 Autoimmunity

Figure 2



Dendritic cells in the initiation and development of autoimmune diabetes. Immature cDC are found in the islets of Langerhans. In the absence of danger or inflammatory signals these DC routinely transport islet-derived antigens to the pancreatic LN. There, these immature DC induce T cell tolerance. Unlike islets of non-diabetes prone mice, islets of NOD mice are infiltrated with pDC, B1a B cells and neutrophils starting around two weeks of age. The physiological beta-cell death that occurs around two weeks of age leads to an accumulation of apoptotic beta cells that are not efficiently cleared in NOD mice. Consequently self-DNA accumulates in the extra-cellular milieu and stimulates the production of anti-DNA IgG by B1a B cells and CRAMP by neutrophils. The resulting complexes engage TLR9 expressed by pDC and induce a burst of IFN α . The cytokine IFN α will induce the maturation of islet-infiltrating cDC, that will then activate in draining LN the islet-reactive CD4 and CD8T cells thus initiating the autoimmune process that will be amplified by the induced, local inflammatory response.

danger sensing molecules may contribute to diabetes in the NOD mice [43]. Recent evidence suggests a major role of TLR9 in diabetes development [40**].

Self-DNA stimulates pDC through TLR9. The islets of NOD mice are infiltrated with pDC starting around two weeks of ages as well as neutrophils and B1a cells [39,40**]. A set of complementary experiments suggests a crosstalk between neutrophil, B1a cells and pDC to generate a local inflammatory response within the islets and ensuing diabetes. Islet organogenesis is associated with a massive physiological beta-cell death around 2–3 weeks of age. Apoptotic cells are inefficiently cleared in NOD mice due to a macrophage defect leading to the persistence of DNA in the extracellular milieu. Diana

et al. showed that this DNA formed complexes with anti-DNA IgG, produced by B1a cells, and neutrophils-derived DNA-binding peptide CRAMP that efficiently stimulated IFN α -production by pancreatic pDC through TLR9 (Figure 2). Blocking IFN α during that time window protected NOD mice from spontaneous diabetes.

In agreement with the role of IFN α in the initiation of type 1 diabetes, anti-IFNRA1 blocking antibodies significantly reduced the incidence and delayed onset of diabetes, an effect that correlated with an increase of immature DC in pancreatic LN [44]. IFN α exerts broad effects on innate and adaptive immunity. Notably IFN α promotes the differentiation of monocyte-derived DC and the maturation of DC, allowing for enhanced and sustained

MHC class II presentation [45,46]. In addition, IFN α favors cross-presentation of exogenous antigens by CD8⁺ DC and consequently CD8T cell responses [47–49]. Enhanced antigen presentation and immunogenicity of DC, and concomitant beta cell death, may lead to the accumulation, in pancreatic LN of cohorts of DC capable of productively activating pathogenic CD4 and CD8T cells, a possibility that need to be explored in more details.

Concluding remarks

Although the puzzle is far from being complete, substantial experimental evidence exists for a pathogenic role of DC in the development of autoimmune disease including type 1 diabetes. Recent studies suggest that beta-cell antigens may undergo post-translational modification, thus creating new self-antigens that are not presented in the thymus. Combined with impaired central tolerance due to TSSP expression in thymic DC these events may significantly increase the autoimmune T cell repertoire to a level that favors autoimmunity.

Evidence also suggests that both genetic and environmental factors may affect beta-cells homeostasis leading to an uncontrolled local inflammatory response that may activate the intra-islet DC, thus preventing peripheral T cell tolerance.

Much work is still needed to define the different environmental factors involved and to understand the molecular interplay between the different DC subsets and other cells of the innate and adaptive immune response that lead to diabetes.

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References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Satpathy AT, Wu X, Albring JC, Murphy KM: **Re(de)fining the dendritic cell lineage.** *Nat Immunol* 2012, **13**:1145–1154.
 2. Merad M, Sathe P, Helft J, Miller J, Mortha A: **The dendritic cell lineage: ontogeny and function of dendritic cells and their subsets in the steady state and the inflamed setting.** *Annu Rev Immunol* 2013, **31**:563–604.
 3. Dresch C, Leverrier Y, Marvel J, Shortman K: **Development of antigen crosspresentation capacity in dendritic cells.** *Trends Immunol* 2012, **33**:381–388.
 4. Reizis B, Bunin A, Ghosh HS, Lewis KL, Sisirak V: **Plasmacytoid dendritic cells: recent progress and open questions.** *Annu Rev Immunol* 2011, **29**:163–183.
 5. Sanos SL, Nowak J, Fallet M, Bajenoff M: **Stromal cell networks regulate thymocyte migration and dendritic cell behavior in the thymus.** *J Immunol* 2011, **186**:2835–2841.
 6. Koble C, Kyewski B: **The thymic medulla: a unique microenvironment for intercellular self-antigen transfer.** *J Exp Med* 2009, **206**:1505–1513.
 7. Gallegos AM, Bevan MJ: **Central tolerance to tissue-specific antigens mediated by direct and indirect antigen presentation.** *J Exp Med* 2004, **200**:1039–1049.
 8. Aschenbrenner K, D'Cruz LM, Vollmann EH, Hinterberger M, Emmerich J, Swee LK, Rolink A, Klein L: **Selection of Foxp3+ regulatory T cells specific for self antigen expressed and presented by Aire+ medullary thymic epithelial cells.** *Nat Immunol* 2007, **8**:351–358.
 9. Hinterberger M, Aichinger M, da Costa OP, Voehringer D, Hoffmann R, Klein L: **Autonomous role of medullary thymic epithelial cells in central CD4(+) T cell tolerance.** *Nat Immunol* 2010, **11**:512–519.
 10. Aichinger M, Wu C, Nedjic J, Klein L: **Macroautophagy substrates are loaded onto MHC class II of medullary thymic epithelial cells for central tolerance.** *J Exp Med* 2013, **210**:287–300.
 11. Coquet JM, Ribot JC, Babala N, Middendorp S, van der Horst G, Xiao Y, Neve JF, Fonseca-Pereira D, Jacobs H, Pennington DJ et al.: **Epithelial and dendritic cells in the thymic medulla promote CD4+Foxp3+ regulatory T cell development via the CD27-CD70 pathway.** *J Exp Med* 2013, **210**:715–728.
 12. Cowan JE, Parnell SM, Nakamura K, Caamano JH, Lane PJ, Jenkinson EJ, Jenkinson WE, Anderson G: **The thymic medulla is required for Foxp3+ regulatory but not conventional CD4+ thymocyte development.** *J Exp Med* 2013, **210**:675–681.
 13. Lei Y, Ripen AM, Ishimaru N, Ohgashi I, Nagasawa T, Jeker LT, Bosl MR, Hollander GA, Hayashi Y, Malefyt Rde W et al.: **Aire-dependent production of XCL1 mediates medullary accumulation of thymic dendritic cells and contributes to regulatory T cell development.** *J Exp Med* 2011, **208**:383–394.
 14. Luche H, Ardouin L, Teo P, See P, Henri S, Merad M, Ginhoux F, Malissen B: **The earliest intrathymic precursors of CD8alpha(+) thymic dendritic cells correspond to myeloid-type double-negative 1c cells.** *Eur J Immunol* 2011, **41**:2165–2175.
 15. Li J, Park J, Foss D, Goldschneider I: **Thymus-homing peripheral dendritic cells constitute two of the three major subsets of dendritic cells in the steady-state thymus.** *J Exp Med* 2009, **206**:607–622.
- This paper presents a detailed kinetic analysis of peripheral DC homing to the thymus. Together with [16*] these papers provided the first indication that peripheral DC may access to the thymus.
16. Bonasio R, Scimone ML, Schaerli P, Grabie N, Lichtman AH, von Andrian UH: **Clonal deletion of thymocytes by circulating dendritic cells homing to the thymus.** *Nat Immunol* 2006, **7**:1092–1100.
- Together with [17*,18*] these papers provide evidence for a role of peripheral DC in ferrying peripheral tissue antigens to the thymus and inducing central tolerance.
17. Hadeiba H, Lahl K, Edalati A, Oderup C, Habtezion A, Pachynski R, Nguyen L, Ghodsi A, Adler S, Butcher EC: **Plasmacytoid dendritic cells transport peripheral antigens to the thymus to promote central tolerance.** *Immunity* 2012, **36**:438–450.
- Together with [16*,18*] these papers provide evidence for a role of peripheral DC in ferrying peripheral tissue antigens to the thymus and inducing central tolerance.
18. Proietto AI, van Dommelen S, Zhou P, Rizzitelli A, D'Amico A, Steptoe RJ, Naik SH, Lahoud MH, Liu Y, Zheng P et al.: **Dendritic cells in the thymus contribute to T-regulatory cell induction.** *Proc Natl Acad Sci U S A* 2008, **105**:19869–19874.
- Together with [16*,17*] these papers provide evidence for a role of peripheral DC in ferrying peripheral tissue antigens to the thymus and inducing central tolerance.
19. Cavanagh LL, Bonasio R, Mazo IB, Halin C, Cheng G, van der Velden AW, Cariappa A, Chase C, Russell P, Starnbach MN et al.: **Activation of bone marrow-resident memory T cells by circulating, antigen-bearing dendritic cells.** *Nat Immunol* 2005, **6**:1029–1037.

6 Autoimmunity

20. Kurts C, Kosaka H, Carbone FR, Miller JF, Heath WR: **Class I-restricted crosspresentation of exogenous self-antigens leads to deletion of autoreactive CD8(+) T cells.** *J Exp Med* 1997, **186**:239-245.
 21. Hsing LC, Rudensky AY: **The lysosomal cysteine proteases in MHC class II antigen presentation.** *Immunol Rev* 2005, **207**:229-241.
 22. Viret C, Leung-Theung-Long S, Serre L, Lamare C, Vignali DA, Malissen B, Carrier A, Guerder S: **Thymus-specific serine protease controls autoreactive CD4 T cell development and autoimmune diabetes in mice.** *J Clin Invest* 2011, **121**:1810-1821.
- This study shows that on the type 1 diabetes susceptible NOD background, the lack of TSSP protects against spontaneous disease. The resistance correlated with altered selection of several islet antigen-specific CD4 T cells mediated by either radioresistant or hemopoietic thymic cells.
23. Viken MK, Blomhoff A, Olsson M, Akselsen HE, Pociot F, Nerup J, Kockum I, Cambon-Thomsen A, Thorsby E, Undlien DE *et al.*: **Reproducible association with type 1 diabetes in the extended class I region of the major histocompatibility complex.** *Genes Immun* 2009, **10**:323-333.
 24. Cheunsuk S, Hsu T, Gershwin ME, Bowls CL: **Analysis of the IDDM candidate gene Prss16 in NOD and NON mice.** *Dev Immunol* 2002, **9**:183-186.
 25. Lie BA, Viken MK, Akselsen HE, Flam ST, Pociot F, Nerup J, Kockum I, Cambon-Thomsen A, Thorsby E, Undlien DE: **Association analysis in type 1 diabetes of the PRSS16 gene encoding a thymus-specific serine protease.** *Hum Immunol* 2007, **68**:592-598.
 26. Lesage S, Hartley SB, Akkaraju S, Wilson J, Townsend M, Goodnow CC: **Failure to censor forbidden clones of CD4 T cells in autoimmune diabetes.** *J Exp Med* 2002, **196**:1175-1180.
 27. Zucchelli S, Holler P, Yamagata T, Roy M, Benoist C, Mathis D: **Defective central tolerance induction in NOD mice: genomics and genetics.** *Immunity* 2005, **22**:385-396.
 28. Liston A, Lesage S, Gray DH, O'Reilly LA, Strasser A, Fahrner AM, Boyd RL, Wilson J, Baxter AG, Gallo EM *et al.*: **Generalized resistance to thymic deletion in the NOD mouse; a polygenic trait characterized by defective induction of Bim.** *Immunity* 2004, **21**:817-830.
 29. Latek RR, Suri A, Petzold SJ, Nelson CA, Kanagawa O, Unanue ER, Fremont DH: **Structural basis of peptide binding and presentation by the type I diabetes-associated MHC class II molecule of NOD mice.** *Immunity* 2000, **12**:699-710.
 30. Mohan JF, Levisetti MG, Calderon B, Herzog JW, Petzold SJ, Unanue ER: **Unique autoreactive T cells recognize insulin peptides generated within the islets of Langerhans in autoimmune diabetes.** *Nat Immunol* 2010, **11**:350-354.
- This study shows for the first time that the Ins9-23 peptide may be presented in different register by DC. This paper also show that the islet environment allows for the presentation of this peptide in a unique conformation thus creating a neo-self antigen.
31. Stadinski BD, Zhang L, Crawford F, Marrack P, Eisenbarth GS, Kappler JW: **Diabetogenic T cells recognize insulin bound to IAg7 in an unexpected, weakly binding register.** *Proc Natl Acad Sci U S A* 2010, **107**:10978-10980.
- Together with [32nd, 33rd], these papers show for the first time that the IAg7 class II molecule may accommodate peptide in different registers. The different binding modes affect the global conformation of the class II/peptide complexes that are differently recognized by distinct CD4 T cells.
32. Mohan JF, Petzold SJ, Unanue ER: **Register shifting of an insulin peptide-MHC complex allows diabetogenic T cells to escape thymic deletion.** *J Exp Med* 2011, **208**:2375-2380.
 33. Stadinski BD, Delong T, Reisdorph N, Reisdorph R, Powell RL, Armstrong M, Piganelli JD, Barbour G, Bradley B, Crawford F *et al.*: **Chromogranin A is an autoantigen in type 1 diabetes.** *Nat Immunol* 2010, **11**:225-231.
 34. Nakayama M, Abiru N, Moriyama H, Babaya N, Liu E, Miao D, Yu L, Wegmann DR, Hutton JC, Elliott JF *et al.*: **Prime role for an insulin epitope in the development of type 1 diabetes in NOD mice.** *Nature* 2005, **435**:220-223.
 35. Delong T, Baker RL, He J, Barbour G, Bradley B, Haskins K: **Diabetogenic T cell clones recognize an altered peptide of chromogranin A.** *Diabetes* 2012, **61**:3239-3246.
- This paper provides the first evidence that the islet-antigen chromogranin A may be subject to post-transcriptional modification for efficient binding to IAg7 class II molecules.
36. Calderon B, Suri A, Miller MJ, Unanue ER: **Dendritic cells in islets of Langerhans constitutively present beta cell-derived peptides bound to their class II MHC molecules.** *Proc Natl Acad Sci U S A* 2008, **105**:6121-6130.
 37. Yin N, Xu J, Ginhoux F, Randolph GJ, Merad M, Ding Y, Bromberg JS: **Functional specialization of islet dendritic cell subsets.** *J Immunol* 2012, **188**:4921-4930.
 38. Melli K, Friedman RS, Martin AE, Finger EB, Miao G, Szot GL, Krummel MF, Tang Q: **Amplification of autoimmune response through induction of dendritic cell maturation in inflamed tissues.** *J Immunol* 2009, **182**:2590-2600.
 39. Welzen-Coppens JM, van Helden-Meeuwssen CG, Leenen PJ, Drexhage HA, Versnel MA: **The kinetics of plasmacytoid dendritic cell accumulation in the pancreas of the NOD mouse during the early phases of insulinitis.** *PLoS ONE* 2013, **8**:e55071.
 40. Diana J, Simoni Y, Furio L, Beaudoin L, Agerberth B, Barrat F, Lehuen A: **Crosstalk between neutrophils B-1a cells and plasmacytoid dendritic cells initiates autoimmune diabetes.** *Nat Med* 2013, **19**:65-73.
- This paper provides an integrated view of the initial events that may induce autoimmune diabetes.
41. Lutz MB, Kurts C: **Induction of peripheral CD4+ T-cell tolerance and CD8+ T-cell cross-tolerance by dendritic cells.** *Eur J Immunol* 2009, **39**:2325-2330.
 42. Saxena V, Ondr JK, Magnusen AF, Munn DH, Katz JD: **The countervailing actions of myeloid and plasmacytoid dendritic cells control autoimmune diabetes in the nonobese diabetic mouse.** *J Immunol* 2007, **179**:5041-5050.
 43. Wen L, Ley RE, Volchkov PY, Stranges PB, Avanesyan L, Stonebraker AC, Hu C, Wong FS, Szot GL, Bluestone JA *et al.*: **Innate immunity and intestinal microbiota in the development of Type 1 diabetes.** *Nature* 2008, **455**:1109-1110.
 44. Li Q, Xu B, Michie SA, Rubins KH, Schreiber RD, McDevitt HO: **Interferon alpha initiates type 1 diabetes in nonobese diabetic mice.** *Proc Natl Acad Sci U S A* 2008, **105**:12439-12440.
 45. Gallucci S, Lolkema M, Matzinger P: **Natural adjuvants: endogenous activators of dendritic cells.** *Nat Med* 1999, **5**:1249-1250.
 46. Simmons DP, Wearsch PA, Canaday DH, Meyerson HJ, Liu YC, Wang Y, Boom WH, Harding CV: **Type I IFN drives a distinctive dendritic cell maturation phenotype that allows continued class II MHC synthesis and antigen processing.** *J Immunol* 2012, **188**:3116-3120.
 47. Diamond MS, Kinder M, Matsushita H, Mashayekhi M, Dunn GP, Archambault JM, Lee H, Arthur CD, White JM, Kalinke U *et al.*: **Type I interferon is selectively required by dendritic cells for immune rejection of tumors.** *J Exp Med* 2011, **208**:1989-1990.
 48. Crespo MI, Zacca ER, Nunez NG, Ranocchia RP, Maccioni M, Maletto BA, Pistoiresi-Palencia MC, Moron G: **TLR7 triggering with polyuridylic acid promotes cross-presentation in CD8alpha+ conventional dendritic cells by enhancing antigen preservation and MHC class I antigen. permanence on the dendritic cell surface.** *J Immunol* 2013, **190**:948-960.
 49. Le Bon A, Etchart N, Rossmann C, Ashton M, Hou S, Gewert D, Borrow P, Tough DF: **Cross-priming of CD8+ T cells stimulated by virus-induced type I interferon.** *Nat Immunol* 2003, **4**:1009-1010.