IDS IMMUNOLOGY OF DIABETES SOCIETY

News Letter

2009 - VOLUME 1, ISSUE 1 (JANUARY TO MARCH)

Dear IDS Members,

This is your first issue of the IDS Newsletter. Here, you will find all the news about IDS, its workshops, annual meetings, proceedings of the meetings published in Annals of the New York Academy of Sciences and abstracts/ new reports on publications connected with autoimmune diabetes.

We have a new website: www.immunologyofdiabetessociety.com
Please visit the website where I plan to archive this and future newsletters.

I hope to bring this to you every quarter. This is a lot of work and I hope I will find time to get this out on every quarter.

We have a new treasurer, Dr.Corrado Cilio, elected unanimously and will serve us to care of the accounts and new memberships. We will soon have an election for the post of Councillor, the seat vacated by Corrado. Please nominate a suitable person for this post. To make the nomination, you should be a member of the IDS and also make sure that you have the nomination seconded by another member.

We have the next annual meeting coming and the abstract deadline is approaching rapidly. You can find the 'flyer' for this meeting in the following pages as well as the latest tentative program for the meeting. For any updates, you will have to check the IDS website.

The Annals of New York Academy of Sciences volume entitled 'Immunology of Diabetes 5: From Bench to Bedside' is already out. I have enclosed the link to the 'Contents page' of this volume in this Newsletter.

Hope you enjoy reading this Newsletter. Wishing you the very best of 2009.

Yours Sincerely

C.B.Sanjeevi

IDS

Immunology of Diabetes Society

www.idsoc.org

10th International Congress of the Immunology of Diabetes Society

May 17-20, 2009

Malmö, Sweden

Information, registration and accommodation:

https://www.registerforevent.net/Register/Pages/Enter.aspx

Event name: ids2009
Password: slagthuset

Abstract deadline: March 3, 2009

Abstract form at: www.immunologyofdiabetessociety.com

Planning Committee Chairs:

Prof. Åke Lernmark, Lund University, Sweden

Assoc. Prof. Corrado M. Cilio, Lund University, Sweden

JDRF Juvenile Diabetes Research Foundation International

National Institutes of Health

Faculty of Medicine Lund University

Malmö stad

Welcome to IDS-10 in Malmö, Sweden May 17-20, 2009

The 10th Immunology of Diabetes Society congress will take place at the Slagthuset Conference Center in Malmö, Sweden. The IDS-10 program will feature as many as 24 Oral Presentations which will be selected from submitted abstracts. In addition, there will be plenty of room for Poster Presentations. The plan is to allow the posters to be featured through the entire meeting and getting participants to come and view the Posters over a glass of wine and cheese. As Immunology of Diabetes is moving fast, the Program Committee wanted more of the Program to be based on novel abstracts rather than of invited speakers. Travel grants to the top abstracts will be offered through funds obtained from the National Institutes of Health and the Juvenile Diabetes Research Foundation.

The Abstract deadline is March 3, 2009 and the abstract form is found on this website under "Abstract Submission". The Scientific Program is approaching the final version (see "Preliminary Programme") and there will be Keynote speakers, Hot Topics, Debates, Symposia as well as DASP and T Cell Workshops. These parts of the Program are intended to provide new information not only from the world of type 1 diabetes research but also lessons-to-be-learned from other areas of immunology research. Daily poster discussions at the Slagthuset Conference Center and other informal activities should provide additional opportunities for scientific interactions to make this conference useful for all.

Malmö is as close to the European continent as you can come in Sweden. The Conference center is easily reached from nearby hotels (go to "Registration" on this website). Please, note the "early bird" conference fee and that you also save on your travel by becoming a member of the IDS.

We look forward to seeing you in Malmö in May 17-20, 2009 and to another exciting and useful IDS Congress.

Welcome!
Åke Lernmark and Corrado M. Cilio

Planning Committee Chairs

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IDS-10 Scientific Program

SUNDAY, MAY 17

08.30	*Antibody workshop* Clinical Research Center (CRC), University Hospital MAS, Malmö
11.00	Light buffet
11.30	Bus to the Conference venue
12.15	*Welcoming Remarks* Å. Lernmark and C. M. Cilio, IDS-10 Co-Chairs T. Delovitch (CAN), IDS President
12.30	*Keynote introductions* Chairman TBN M. von Herrath USA A. Green UK
13.30	BREAK (Coffee, fruit and refreshments)
14.00	*Oral Presentations I* Chairpersons: TBN
15.30	*Hot topics – 1: Immunoregulation* C. Benoist USA (Moderator) T. Saito, JPN C. Hampe, USA C. King, AUS
17.00-19.00	*Poster viewing and discussion I (wine & cheese)*
20.00	Get-together reception (Malmö City)
22.00	Late bar with music and scientific topics

MONDAY, MAY 18

08.30	*Oral Presentations II* Chairpersons: TBN
09.30	*Hot topics – 2: T1D genes: humans– mice –rats* G. Eisenbarth USA (Moderator) J. Danska CAN T1DGC report: F. Pociot DK
10.30	BREAK (Coffee, fruit and refreshments)
11.00	*Debate 1: Type 1 diabetes genes – needed or not?* E. Gale UK (Moderator), G.T. Nepom USA vs S. Rich USA
12.00	LUNCH
13.00	*Hot topics-3: Combination therapy* J. Krisher USA (Moderator) C. Greenbaum USA D. Harlan USA
14.00	*Oral Presentations III* Chairpersons: TBN
15.00	Antibody Workshop (DASP) Report
15.30	BREAK (Coffee, fruits and refreshments)
16.00	*JDRF Symposium: Antigen-specific therapies* R. Insel USA (Moderator) S. D. Miller USA M. Peakman UK P. Santamaria CAN M. Czech USA
18.00-19.00	*Poster II (wine & cheese)*
20.00	*IDS gala dinner, Congress venue*

TUESDAY, MAY 19

08.30	*T Cell Workshop (TDEVI)*
10.30	BREAK (Coffee, fruit and refreshments)
11.00	*Oral Presentations IV* Chairpersons: TBN
12.00	LUNCH
13.00	*Hot topics-4: Beta cell regeneration and stem cells* H. Semb SE (Moderator) H. Heimberg BE O. Madsen DK
14.00	*Innate and adaptive immunity Symposium* T. Delovitch (Moderator) T. Delovitch CAN G. de Libero CH B. Pulendran USA
15.30	BREAK (Coffee, fruit and refreshments)
16.00	*Debate 2: How much type 1 is type 2 diabetes?* Å. Lernmark SE (Moderator) L. Groop SE vs J. Palmer USA
17.00	**IDS Business Meeting**
18.00- 20.00	*Poster III (wine & cheese)* *Industry presentations & buffet*
21.00	Late bar with T Cell Karaoke

WEDNESDAY, MAY 20

08.30	*New Biomarkers Symposium* M. Atkinson USA (Moderator) M. Hessner USA M. Oresic FIN D. Eizirik BE
10.00	BREAK (Coffee, fruit and refreshments)
10.30	*Oral presentation V* Chairpersons: TBN
12.00	LUNCH
13.00	*Allergy & Autoimmunity Symposium* C.M. Cilio SE (Moderator) M. S. Anderson USA C. Akdis CH
14.00	*Concluding Remarks* O. Kämpe SE
14.30	*IDS-11 invitation*
15.00	*End of meeting*
	Farewell refreshments

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ABSTRACT FORM

Deadline for submission of abstracts: March 3th, 2009

PRESENTING AUTHOR: **DATE:**

INSTITUTION:

DEPARTMENT:

TELEPHONE : **EMAIL:**

IDS membership No:

Oral Presentation ☐ **Poster Presentation** ☐ **Late breaking news** ☐

IDS-10 Award: ☐ **yes** ☐ **no** **year of birth:**

ABSTRACT FORM INSTRUCTIONS

1) Each abstract must be written in English, maximum length 250 words, with Times New Roman, in 12p font. It must be contained within the box space. Do not type outside the margin.
2) The title of the abstract must be typed with capital letters and the name of the presenting authors must be underlined.
3) The text is to be structured according to the following layout: a) **Background/rational**: describe the main aim of the study b) **Methods**: include the description of applied methods, data collection procedures and statistical tests used c) **Results**: they must be documented with enough detail to justify conclusion; c) **Conclusion**: describe briefly implication deriving from results obtained.
4) Abstract not complying with these rules will not be admitted to selection.
5) The presenting author must be registered to the Congress and be a paid-up member of the IDS

Application for Travel Grant

The IDS-10 Congress offers a limited number of IDS-10 Awards for the best abstracts. The IDS-10 Award will be sufficient to cover the registration fee and part of the costs for travel and accommodation.

The IDS-10 Award will be selected buy the Scientific Program Committee based on the submitted abstracts. The Scientific Program Committee will rate the abstracts on a scale from 1-5 where 5 is the best. The winners of the IDS-10 Award will be notified ahead of the meeting or no later than April 15, 2009. The winners of the IDS-10 Award will be announced at the Opening of the meeting and in the printed program.

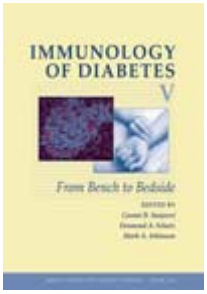
The recipient of an IDS-10 Award:

1) has checked the IDS-10 Award box on the Abstract form
2) is the presenting author
3) is paid up member of IDS
4) is younger than 35 years of age i.e. born after January 1, 1974.

BECOME A MEMBER OF IDS

Become a member now and take advantage of the low registration fee. To become a member, please visit http://www.immunologyofdiabetessociety.com/. Click on the link 'membership' and follow the instructions to pay online.

ANNALS of
The New York Academy of Sciences



Immunology of Diabetes V

Edited by: Carani B. Sanjeevi (Center for Molecular Medicine, Karolinska Institute, Stockholm, Sweden); Desmond A. Schatz (University of Florida College of Medicine, Gainesville, Florida); Mark A. Atkinson (University of Florida College of Medicine, Gainesville, Florida)

This volume is an overview of current research in the field of immunology as it relates to diabetes. Topics covered include: autoantibody markers for type 1 diabetes; cellular immune markers for type 1 diabetes; animal models of type 1 diabetes; the pancreas in type 1 diabetes; genetics of type 1 diabetes; the role of toll-like receptors and innate immunity in type 1 diabetes; cell-based therapies for type 1 diabetes; environmental and mechanistic causes of type 1 diabetes; mechanisms of beta-cell death; role of the immune response in type 1 diabetes; and islet transplantation.

Read the article "***Immunoregulatory Pathways Controlling Progression of Autoimmunity in NOD Mice***" by **Sylvaine You, Marie-Alexandra Alyanakian, et al.** online - free for a limited time.

To read the full table of contents for this volume, click here

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THE DIABETES NEWS-I

CONTENTS

GENETICS

1. IL2RA genetic heterogeneity in multiple sclerosis and type 1 diabetes susceptibility and soluble interleukin-2 receptor production

Multiple Sclerosis (MS) and type 1 diabetes (T1D) are organ-specific autoimmune disorders with significant heritability, part of which is conferred by shared alleles. For decades, the Human Leukocyte Antigen (HLA) complex was the only known susceptibility locus for both T1D and MS, but loci outside the HLA complex harboring risk alleles have been discovered and fully replicated. A genome-wide association scan for MS risk genes and candidate gene association studies have previously described the IL2RA gene region as a shared autoimmune locus. In order to investigate whether autoimmunity risk at IL2RA was due to distinct or shared alleles, we performed a genetic association study of three IL2RA variants in a DNA collection of up to 9,407 healthy controls, 2,420 MS, and 6,425 T1D subjects as well as 1,303 MS parent/child trios. Here, we report "allelic heterogeneity" at the IL2RA region between MS and T1D. We observe an allele associated with susceptibility to one disease and risk to the other, an allele that confers susceptibility to both diseases, and an allele that may only confer susceptibility to T1D. In addition, we tested the levels of soluble interleukin-2 receptor (sIL-2RA) in the serum from up to 69 healthy control subjects, 285 MS, and 1,317 T1D subjects. We demonstrate that multiple variants independently correlate with sIL-2RA levels.

Source: Maier LM et al. PLoS Genet. 2009 Jan;5(1):e1000322. Epub 2009 Jan 2

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2. Type 1 diabetes in the BB rat: A Polygenic Disease

Objective: Two type 1 diabetes (T1D) susceptibility genes have been identified in the spontaneously diabetic BBDP rat, the MHC (RT1) Class II u haplotype (Iddm1), and Gimap5 (Iddm2). The strong effects of these have impeded previous efforts to map additional loci. We tested the hypothesis that T1D is a polygenic disease in the BBDP rat. Research Design and Methods: We performed the most comprehensive genome-wide linkage analysis for T1D, age of disease onset (AOO), and insulitis sub-phenotypes in 574 F2 animals from a cross-intercross between BBDP and T1D-resistant, double congenic ACI.BBDP-RT1u,GIMAP5 (ACI.BB(1u.lyp)) rats, where both Iddm1 and Iddm2 were fixed as BBDP.

Results: Nineteen percent of these F2 animals developed T1D, and eight T1D susceptibility loci were mapped, six showing significant linkage (chromosomes 1, 3, 6(two loci), 12, and 14) and two (chromosomes 2 and 17), suggestive linkage. The chromosomes 6, 12, and 14 intervals were also linked to the severity of islet infiltration by immunocytes, while those on chromosomes 1, 6(two loci), 14, 17, and a T1D-unlinked chromosome 8 interval showed significant linkage to the degree of islet atrophy. Four loci exhibited suggestive linkage to AOO on chromosomes 2(two loci), 7 and 18 but were unlinked to T1D. INS, PTPN22, IL2/IL21, C1QTNF6 and C12orf30 associated with human T1D, are contained within the chromosomes 1, 2, 7 and 12 loci.

Conclusions: This study demonstrates that the BBDP diabetic syndrome is a complex, polygenic disease that may share additional susceptibility genes beside MHC Class II, with human T1D.

Source: Wallis RH et al. Diabetes. 2009 Jan 23. [Epub ahead of print].

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3. Three microsatellites from the T1DGC MHC data set show highly significant association with type 1 diabetes, independent of the HLA-DRB1, -DQA1 and -DQB1 genes.

AIM: The aim of this study was to test the microsatellites in the Type 1 Diabetes Genetics Consortium major histocompatibility complex (MHC) data set for association with type 1 diabetes (T1D) independent of the HLA-DRB1, -DQA1 and -DQB1 genes.

METHODS: The data set was edited to contain only one affected child per family, and broad ethnic subgroups were defined. Genotypes for HLA-DRB1, -DQA1 and -DQB1 were replaced by a haplotype code spanning all three loci, with phase inferred based on common haplotypes. The final data set contained 8190 samples in 2301 families, 59 microsatellites and the DRB1-DQA1-DQB1 haplotype code. Statistical analyses consisted of conditional logistic regression and haplotype estimations and linkage disequilibrium calculations.

RESULTS: The data set was screened using a main effects test approach adjusted for DRB1-DQA1-DQB1, and significant results tested for validity. After these procedures, four markers remained significant at the Bonferroni-corrected threshold: D6S2773 (p = 0.00014), DG6S185 (p = 0.00015), DG6S398 (p = 0.00043) and D6S2998 (p = 0.00015). These results were

supported by allelic tests conditioned on DRB1-DQA1-DQB1 haplotypes, except for DG6S185, which may contain artefacts.

CONCLUSIONS: We have identified three microsatellites that mark additional risk factors for T1D at highly significant levels in the MHC. Further analyses are needed to establish the relationship with other possible genetic determinants in this region.

Source: Eike MC, Humphreys K, Becker T, Olsson M, Lie BA; Diabetes Genetics Consortium. Diabetes Obes Metab. 2009 Feb;11 Suppl 1:17-24.

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4. Association of MHC SNP genotype with susceptibility to type 1 diabetes: a modified survival approach.

AIM: The Major Histocompatibility Complex (MHC) is a highly polymorphic region on chromosome 6 encompassing the human leucocyte antigen (HLA)-DQ/DR loci most predictive of susceptibility to type 1 diabetes (T1D). To assess the contribution of other MHC genes, in this exploratory analysis of Type 1 Diabetes Genetics Consortium (T1DGC) family data we characterize association between susceptibility and MHC single nucleotide polymorphism (SNP) genotype, with an emphasis on effects of genetic variation additional to carriage of predisposing or protective MHC haplotypes.

METHODS: We use Cox regression analyses of age of onset, stratified by family, to jointly test both linkage and association. Analysis is restricted to children from families having both affected and unaffected siblings and is conducted with and without adjustment for known HLA class I and II effects. Model fits provide scores for each individual that are based on estimates of the probability of being affected by the age of 35, given the individual's SNP genotype. The mean within-family variation in these scores provides a measure that closely reflects the relative size of the likelihood ratio test statistics, and their covariation provides a means of mapping patterns of association that incorporate both effect size and commonality of effect that is attributable to the strong linkage disequilibrium (LD) extending across the region.

RESULTS: Univariate analyses yielded strong associations with T1D susceptibility that are dominated by SNPs in the class II HLA-DR/DQ region but extend across the MHC. Similar effects are frequently observed across SNPs within multiple genes, sometimes spanning hundreds of

kilobases. SNPs within a region at the telomeric end of the class II gene HLA-DRA yielded significant associations with and without adjustment for carriage of the predictive DR3, DR4, DR2 and DR7 HLA haplotypes, and remained highly prominent in a secondary analysis that was restricted to 66 families in whom at least one of the affected siblings carried neither the DR3 nor DR4 haplotype.

CONCLUSIONS: While many of the associations can be attributed to LD between the SNPs and the dominant HLA-DRB/DQA/DQB loci, there is also evidence of additional modifying effects.

Source: Diabetes Obes Metab. 2009 Feb;11 Suppl 1:92-100.

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5. Missingness in the T1DGC MHC fine-mapping SNP data: association with HLA genotype and potential influence on genetic association studies.

AIM: The absence or 'missingness' of single nucleotide polymorphism (SNP) assay values because of genotype or related factors of interest may bias association and other studies. Missingness was determined for the Type 1 Diabetes Genetics Consortium (T1DGC) Major Histocompatibility Complex (MHC) data and was found to vary across the region, ranging up to 11.1% of the non-null proband SNPs, with a median of 0.3%. We consider factors related to missingness in the T1DGC data and briefly assess its possible influence on association studies.

METHODS: We assessed associations of missingness in the SNP assay data with human leucocyte antigen (HLA) genotype of the individual and with SNP genotypes of the parents. Within-cohort analyses were combined (over all cohorts) using (i) Mantel-Haenszel tests for two-by-two tables or (ii) by combining test statistics for larger tables and regression models. Mixed effect regression models were used to assess association of the SNP genotypes with affected status of the offspring after adjustment for parental SNP genotypes, cohort membership and HLA genotypes. Log-linear models were used to assess association of missingness in the unaffected sib assays with SNP genotypes of the probands.

RESULTS: Missingness of SNP values near the HLA class I (A, B and C) and class II (DR, DQ and DP) loci is strongly associated with carriage of corresponding HLA genotypes within these groups. Similar associations pertain to missing values among the microsatellite data. In at least some of these cases, regions of missingness coincided with known deletion regions

corresponding to the associated HLA haplotype. We conjecture that other regions of associated missingness may point to similar haplotypic deletions. Analysis of association patterns of SNP genotypes with affected status of offspring does not indicate strong informative missingness. However, association of missingness in proband data with parental SNP genotypes may impact transmission disequilibrium test (TDT)-type analyses. Comparisons of affected and unaffected siblings point to possible susceptibility regions additional to the classical HLA-DR3/4 alleles near BAT4-LY6G5B-BAT5 and NOTCH4.

CONCLUSIONS: Potentially informative missingness in SNP assay values in the MHC region may impact on association and related analyses based on the T1DGC data. These results suggest that it would be prudent to assess the degree to which missingness may abrogate assessed SNP disease markers in such studies. Initial analyses based on comparison of affected and unaffected status in offspring suggest that at least these may be little affected.

Source: James I, McKinnon E, Gaudieri S, Morahan G; Diabetes Genetics Consortium. Diabetes Obes Metab. 2009 Feb;11 Suppl 1:101-7.

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6. Shared and distinct genetic variants in type 1 diabetes and celiac disease.

BACKGROUND: Two inflammatory disorders, type 1 diabetes and celiac disease, cosegregate in populations, suggesting a common genetic origin. Since both diseases are associated with the HLA class II genes on chromosome 6p21, we tested whether non-HLA loci are shared.

METHODS: We evaluated the association between type 1 diabetes and eight loci related to the risk of celiac disease by genotyping and statistical analyses of DNA samples from 8064 patients with type 1 diabetes, 9339 control subjects, and 2828 families providing 3064 parent-child trios (consisting of an affected child and both biologic parents). We also investigated 18 loci associated with type 1 diabetes in 2560 patients with celiac disease and 9339 control subjects.

RESULTS: Three celiac disease loci--RGS1 on chromosome 1q31, IL18RAP on chromosome 2q12, and TAGAP on chromosome 6q25--were associated with type 1 diabetes (P<1.00x10(-4)). The 32-bp insertion-deletion variant on chromosome 3p21 was newly identified as a type 1 diabetes locus (P=1.81x10(-8)) and was also associated with celiac disease, along with PTPN2 on chromosome 18p11 and CTLA4 on chromosome 2q33, bringing the total number of loci with evidence of a shared association to seven, including SH2B3 on chromosome 12q24. The effects

of the IL18RAP and TAGAP alleles confer protection in type 1 diabetes and susceptibility in celiac disease. Loci with distinct effects in the two diseases included INS on chromosome 11p15, IL2RA on chromosome 10p15, and PTPN22 on chromosome 1p13 in type 1 diabetes and IL12A on 3q25 and LPP on 3q28 in celiac disease.

CONCLUSIONS: A genetic susceptibility to both type 1 diabetes and celiac disease shares common alleles. These data suggest that common biologic mechanisms, such as autoimmunity-related tissue damage and intolerance to dietary antigens, may be etiologic features of both diseases.

Source: Smythe DJ et al. N Engl J Med. 2008 Dec 25; 359(26): 2767-77. Epub 2008 Dec 10.

IMMUNOLOGY

7. Review series on helminths, immune modulation and the hygiene hypothesis: how might infection modulate the onset of type 1 diabetes?

The development of type 1 diabetes is influenced by both genetic and environmental factors. The current rise in the incidence of diabetes is occurring more rapidly than can be accounted for by genetic change, highlighting the influence of environmental modifiers. Considerable effort has been expended to identify infectious agents that might be responsible for this rise in incidence, but no single infectious agent has been linked to this dramatic increase in type 1 diabetes. There has been increasing interest in the possibility that infections of historical importance that might have shaped our immune systems over evolutionary time may also have played a role in down-modulating some autoimmune and allergic disorders. In this review, some of the ways in which certain organisms might have influenced the onset of autoimmunity are discussed.

Source: Cooke A., Immunology. 2009 Jan;126(1):12-7

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8. Heat-shock proteins can promote as well as regulate autoimmunity.

Heat-shock proteins (Hsps) are among the most highly conserved and immunogenic proteins shared by microbial agents and mammals. Under physiological conditions, the ubiquitously distributed Hsps maintain the integrity and function of other cellular proteins when cells are exposed to stressful stimuli. However, owing to their conserved nature and stress inducibility, Hsps may become targets of immune response. The T cells and/or antibodies induced by a microbial Hsp may crossreact with the corresponding mammalian Hsp (molecular mimicry) and trigger an autoimmune response, which if unchecked can lead to immune pathology and clinical manifestations. Furthermore, enhanced expression of Hsp under stress can unveil previously hidden antigenic determinants that can initiate and perpetuate autoimmune reactivity. Also, the innate immune mechanisms activated by an Hsp can reinforce and even direct the type of adaptive immune response to that protein. Hsps have been implicated in the induction and propagation of autoimmunity in several diseases, including rheumatoid arthritis, atherosclerosis and type 1 diabetes. However, Hsps possess immunoregulatory attributes as well and therefore, are being exploited for immunomodulation of various immune-mediated disorders.

Source: Rajaiah R, Moudgil KD**.** Autoimmun Rev. 2008 Dec 30. [Epub ahead of print].

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9. Can we learn from viruses how to prevent type 1 diabetes? : the role of viral infections in the pathogenesis of type 1 diabetes and the development of novel combination therapies.

We will take a journey from basic pathogenetic mechanisms elicited by viral infections that play a role in the development of type 1 diabetes to clinical interventions, where we will discuss novel combination therapies. The role of viral infections in the development of type 1 diabetes is a rather interesting topic because in experimental models viruses appear capable of both accelerating as well as decelerating the immunological processes leading to type 1 diabetes. Consequently, I will discuss some of the underlying mechanisms for each situation and consider methods to investigate the proposed dichotomy for the involvement of viruses in human type 1 diabetes. Prevention of type 1 diabetes by infection supports the so-called "hygiene hypothesis." Interestingly, viruses invoke mechanisms that need to be exploited by novel combinatorial immune-based interventions, the first one being the elimination of autoaggressive T-cells attacking the beta-cells, ultimately leading to their immediate but temporally limited amelioration. The other is the invigoration of regulatory T-cells (Tregs), which can mediate long-term tolerance to beta-cell proteins in the pancreatic islets and draining lymph nodes. In combination, these two immune elements have the potential to permanently stop type 1 diabetes. It is my belief that only combination therapies will enable the permanent prevention and curing of type 1 diabetes.

Source: von Herrath M. Diabetes. 2009 Jan;58(1):2-11

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10. Toll-like receptor 3 signaling on macrophages is required for survival following coxsackievirus B4 infection.

Toll-like receptor 3 (TLR3) has been proposed to play a central role in the early recognition of viruses by sensing double stranded RNA, a common intermediate of viral replication. However, several reports have demonstrated that TLR3 signaling is either dispensable or even harmful following infection with certain viruses. Here, we asked whether TLR3 plays a role in the

response to coxsackievirus B4 (CB4), a prevalent human pathogen that has been associated with pancreatitis, myocarditis and diabetes. We demonstrate that TLR3 signaling on macrophages is critical to establish protective immunity to CB4. TLR3 deficient mice produced reduced pro-inflammatory mediators and are unable to control viral replication at the early stages of infection resulting in severe cardiac damage. Intriguingly, the absence of TLR3 did not affect the activation of several key innate and adaptive cellular effectors. This suggests that in the absence of TLR3 signaling on macrophages, viral replication outpaces the developing adaptive immune response. We further demonstrate that the MyD88-dependent signaling pathways are not only unable to compensate for the loss of TLR3, they are also dispensable in the response to this RNA virus. Our results demonstrate that TLR3 is not simply part of a redundant system of viral recognition, but rather TLR3 plays an essential role in recognizing the molecular signatures associated with specific viruses including CB4.

Source: Richer MJ, Lavallée DJ, Shanina I, Horwitz MS. PLoS ONE. 2009;4(1):e4127. Epub 2009 Jan 5.

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11. Th17 cells promote pancreatic inflammation but only induce diabetes efficiently in lymphopenic hosts after conversion into Th1 cells.

IDDM is characterized by leukocyte invasion to the pancreatic tissues followed by immune destruction of the islets. Despite the important function of Th17 cells in other autoimmune disease models, their function in IDDM is relatively unclear. In this study, we found association of elevated Th17 cytokine expression with diabetes in NOD mice. To understand the function of Th17 cells in IDDM, we differentiated islet-reactive BDC2.5 TcR transgenic CD4(+) cells in vitro into Th17 cells and transferred them into NOD.scid and neonate NOD mice. NOD.scid recipient mice developed rapid onset of diabetes with extensive insulitic lesions, whereas in newborn NOD mice, despite extensive insulitis, most recipient mice did not develop diabetes. Surprisingly, BDC2.5(+) cells recovered from diabetic NOD.scid mice, in comparison with those from neonate NOD mice, showed predominant IFN-gamma over IL-17 expression, indicating conversion of donor cells into Th1 cells. Moreover, diabetes progression in NOD.scid recipients was dependent on IFN-gamma while anti-IL-17 treatment reduced insulitic inflammation. These results indicate that islet-reactive Th17 cells promote pancreatic inflammation, but only induce IDDM upon conversion into IFN-gamma producers.

Source: Martin-Orozco N et al. Eur J Immunol. 2009 Jan; 39(1) :216-24

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12. Soluble IL-2RA levels in multiple sclerosis subjects and the effect of soluble IL-2RA on immune responses.

Multiple sclerosis (MS) is an organ-specific autoimmune disorder that is in part genetically determined. The gene encoding the alpha-chain of the IL-2 receptor, IL2RA, harbors alleles associated with risk to MS and other autoimmune diseases. In addition, IL2RA genetic variants correlate with the levels of a soluble form of the IL-2 receptor in subjects with type 1 diabetes and multiple sclerosis. Here, we show that the IL2RA genotypes differentially affects soluble IL-2RA (sIL-2RA) levels in MS cases vs healthy controls; the two variants associated with MS (rs12722489 and rs2104286) account for 15 and 18% of the total variance in log(10)-transformed sIL-2RA concentration in control subjects but less so in subjects with MS (2 and 5%), suggesting that perturbations associated with disease or treatment may influence sIL-2RA levels in subjects with MS. Whereas analyses demonstrate that sIL-2RA serum concentrations are a remarkably stable phenotype in both healthy controls and untreated MS subjects, a difference is observed between benign and malignant MS. These data indicate that, in addition to specific allelic variants at IL2RA, immunological perturbations associated with aggressive forms of the disease can influence sIL-2RA levels in serum of MS subjects. We also demonstrate, functionally, that sIL-2RA can inhibit IL-2 signaling, yet enhance T cell proliferation and expansion. In summary, we propose that before disease onset, strong genetic factors associated with disease risk dictate sIL-2RA levels that may be further modulated with onset of chronic systemic inflammation associated with MS

Source: Maier LM, Anderson DE, Severson CA, Baecher-Allan C, Healy B, Liu DV, Wittrup KD, De Jager PL, Hafler DA. J Immunol. 2009 Feb 1;182(3):1541-7.

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13. CD103 is dispensable for anti-viral immunity and autoimmunity in a mouse model of virally-induced autoimmune diabetes.

Recent studies suggest a beneficial role for blocking CD103 signaling in preventing islet allograft rejection and thus Type 1 diabetes (T1D) in non-obese diabetic (NOD) mice. However, antibody blockade approaches generally raise anti-microbial safety issues, necessitating additional studies to address the possible adverse effects of antibody therapy. Here we report that CD103 had no significant impact on the development of primary and memory CD8(+) or CD4(+) responses after acute lymphocytic choriomeningitis virus (LCMV) infection. In addition, CD103 was found to be dispensable for T1D progression in a rapid, CD8-mediated virally-induced T1D model (the rat

insulin promoter [RIP]-LCMV), suggesting that its previous efficacy in the NOD mouse model may not be related to its effect on the generation, memory conversion and/or effector function of CD8(+) or CD4(+) T cells. While the data does not preclude a role for CD103 in T1D in its entirety, the current study does provide much evidence to suggest that CD103 blockade may prove to be a safe intervention for autoimmunity and allo-transplantation. While in cases of rapid microbial (CD8)-driven T1D CD103 antibody blockade may not limit disease progression or severity, in mucosally-driven cases of T1D anti-CD103 antibody treatment may provide a new and safe therapeutic avenue.

Source: Fousteri G, Dave A, Juntti T, von Herrath M. J Autoimmun. 2009 Feb;32(1):70-7. Epub 2009 Jan 21

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14. Modulation of dendritic cells using granulocyte-macrophage colony-stimulating factor (GM-CSF) delays type 1 diabetes by enhancing CD4+CD25+ regulatory T cell function.

Abnormalities in DC function are implicated in defective immune regulation that leads to type-1 diabetes (T1D) in NOD mice and humans. In this study, we used GM-CSF and Flt3-L to modulate DC function in NOD mice and observed the effects on T1D development. Treatment with either ligand at earlier stages of insulitis suppressed the development of T1D. Unlike Flt3-L, GM-CSF was more effective in suppressing T1D, even when administered at later stages of insulitis. In vitro studies and in vivo adoptive transfer experiments revealed that CD4+CD25+ T cells from GM-CSF-treated mice could suppress effector T cell response and T1D. This suppression is likely mediated through enhanced IL-10 and TGF-beta1 production. Adoptive transfer of GM-CSF exposed DCs to naive mice resulted in an expansion of Foxp3+ T cells and a significant delay in T1D onset. Our results indicate that GM-CSF acted primarily on DCs and caused an expansion of Foxp3+ Tregs which delayed the onset of T1D in NOD mice.

Source: Cheatem D, Ganesh BB, Gangi E, Vasu C, Prabhakar BS. Clin Immunol. 2009 Jan 24. [Epub ahead of print].

TREATMENT

15. GAD65 autoimmunity-clinical studies.

Type 1 diabetes (T1D) in children and particularly in teenagers and adults is strongly associated with autoreactivity to the Mr 65,000 isoform of glutamic acid decarboxylase (GAD65). Autoantibodies to GAD65 are common at the time of clinical diagnosis and may be present for years prior to the onset of hyperglycemia. GAD65 autoantibodies predict conversion to insulin dependence when present in patients classified with type 2 diabetes nowadays more often referred to as patients with latent autoimmune diabetes in the adult (LADA) or type 1,5 diabetes.

Analyses of T cells with HLA DRB1 0401-tetramers with GAD65-specific peptides as well as of anti-idiotypic GAD65 autoantibodies suggest that GAD65 autoreactivity is common. The immunological balance is disturbed and the appearance of GAD65 autoantibodies represents markers of autoreactive loss of pancreatic beta cells. Extensive experimental animal research, in particular of the Non-obese diabetic (NOD) mouse, showed that GAD65 therapies reduce insulitis and prevent spontaneous diabetes. Recombinant human GAD65 produced by current Good Manufacturing Practice (cGMP) and formulated with alum was found to be safe in Phase I and II placebo-controlled, double-blind, randomized clinical trials.

The approach to modulate GAD65 autoreactivity with subcutaneous immunotherapy (SCIT) showed promise as alum-formulated GAD65 induced a dose-dependent reduction in the disappearance rate of endogenous residual C-peptide production. Additional controlled clinical trials are needed to uncover the mechanisms by which subcutaneous injections of recombinant human GAD65 may alter GAD65 autoreactivity.

Source: Uibo R, Lernmark A. Adv Immunol. 2008;100:39-78.

TRANSPLANTATION

16. Islet transplantation with alemtuzumab induction and calcineurin-free maintenance immunosuppression results in improved short- and long-term outcomes.

BACKGROUND: Only a minority of islet transplant recipients maintain insulin independence at 5 years under the Edmonton protocol of immunosuppression. New immunosuppressive strategies are required to improve long-term outcomes. MATERIALS AND

METHODS: Three subjects with unstable type 1 diabetes mellitus underwent islet transplantation with alemtuzumab induction and sirolimus-tacrolimus maintenance for 3 months and then sirolimus-mycophenolic acid maintenance thereafter. Follow-up was more than 2 years. Comparison was with 16 historical subjects transplanted under the Miami version of the Edmonton protocol.

RESULTS: Insulin independence was achieved in 2 of 3 alemtuzumab and 14 of 16 historical subjects. Those who did not achieve insulin independence only received a single islet infusion. Insulin-independence rates remained unchanged in the alemtuzumab group, but decreased from 14 of 16 (88%) to 6 of 16 (38%) in the historical group over 2 years. Insulin requirements increased in the historical group while remaining stable in the alemtuzumab group. Comparison of functional measures at 3 months suggested better engraftment with alemtuzumab (P=NS). Further comparison of alemtuzumab versus historical groups, up to 24 months, demonstrated significantly better: Mixed meal stimulation index (24 months, 1.0+/-0.08 [n=3] vs. 0.5+/-0.06 pmol/mL [n=6], P<0.01), mixed meal peak C-peptide (24 months, 5.0+/-0.5 [n=3] vs. 3.1+/-0.3 nmol/mL [n=6], P<0.05), HbA1c (24 months, 5.4+/-0.15 [n=3] vs. 6.3+/-0.12 pmol/mL [n=10], P<0.01). Administration of alemtuzumab was well tolerated. There was no increased incidence of infections in alemtuzumab subjects despite profound, prolonged lymphocyte depletion.

CONCLUSIONS: Islet transplantation with alemtuzumab induction was well tolerated and resulted in improved short- and long-term outcomes. Further investigation is underway for validation.

Source: Froud T, Baidal DA, Faradji R, Cure P, Mineo D, Selvaggi G, Kenyon NS, Ricordi C, Alejandro R. Transplantation. 2008 Dec 27;86(12):1695-701

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17. Long-term insulin independence and improvement in insulin secretion after supplemental islet infusion under exenatide and etanercept

BACKGROUND: Progressive graft dysfunction (GDF) and loss of insulin independence (II) have been invariably observed in islet transplant recipients under the "Edmonton protocol." To reestablish II, we performed supplemental islet infusions (SI) in recipients of allogeneic islet transplant alone, displaying GDF. To improve the engraftment and long-term graft function of SI, exenatide (EXN) and etanercept treatment at islet infusion, and long-term EXN treatment were tested in a non-randomized pilot clinical trial.

METHODS: Patients with GDF received SI under Edmonton-like immunosuppression with daclizumab induction, either without interventions (SI-control; n=5) or with EXN and etanercept treatment (SI-EXN; n=4). Clinical and metabolic profiles were assessed during 18-month follow-up.

RESULTS: Long-term II (18 months) was observed in 100% of SI-EXN and in 20% of SI-control (P=0.04). SI-EXN subjects demonstrated restoration of function better than that seen after initial islet infusions. Comparison of SI-EXN and SI-control groups demonstrated better responses in SI-EXN subjects at 3 months post-SI. During the 18 months of follow-up, function was sustained in the SI-EXN subjects better than in SI-controls. Acute effects of EXN during mixed meal tolerance test and intravenous glucose tolerance test results in improved first and second phase insulin release in response to intravenous glucose tolerance test and suppressed postprandial hyperglucagonemia after mixed meal tolerance test.

CONCLUSION: These results suggest that the combination of EXN and etanercept improve engraftment and long-term islet survival and function in subjects undergoing SI. This data, however, must be interpreted with some caution because of small sample size, lack of randomization, and sequential comparison with historical controls.

Source: Faradji RN et al. Transplantation. 2008 Dec 27; 86 (12): 1658 - 65.

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18. Upregulating CD4+CD25+FOXP3+ regulatory T cells in pancreatic lymph nodes in diabetic NOD mice by adjuvant immunotherapy

BACKGROUND: Immunotherapy with Complete Freund's adjuvant (CFA) is effective in ameliorating autoimmunity in diabetic nonobese diabetic (NOD) mice. We investigated whether CFA treatment up-regulates CD4+CD25+Foxp3+ regulatory T cells and increases transforming growth factor (TGF)-beta1 production in diabetic NOD mice.

METHODS: New-onset diabetic NOD mice were treated with CFA and exendin-4, a potent analog of glucagon-like peptide-1. Reversal of diabetes was determined by monitoring blood glucose level. Ameliorating autoimmunity through immunoregulation was assessed by adoptive transfer. Regulatory T cells in the peripheral blood, spleen, thymus, and pancreatic nodes were measured. TGF-beta1 in plasma and the insulin content in the pancreas were also measured. Immunostainings for insulin and BrdU were performed.

RESULTS: New-onset diabetes could be reversed in 38% of NOD mice treated with CFA alone and in 86% of NOD mice treated with both CFA and exendin-4. Diabetes adoptive transfer by splenocytes from CFA-treated NOD mice was delayed. The percentage of CD4+CD25+Foxp3+ regulatory T cells in the pancreatic lymph nodes of CFA-treated NOD mice was significantly increased at 1, 5, and 15 to 17 weeks after treatment. TGF-beta1 in the plasma of CFA-treated NOD mice was also significantly increased. Combining CFA with exendin-4 treatment significantly increased the insulin content and the numbers of insulin and BrdU double-labeled beta cells in the islets.

CONCLUSIONS: Our results demonstrated that CFA treatment ameliorates autoimmunity in diabetic NOD mice by up-regulating CD4=CD25+Foxp3+ regulatory T cells and increasing TGF-beta1 production. Exendin-4 enhanced the effect of CFA on reversing diabetes in NOD mice by stimulating beta-cell replication.

Source: Tian B et al. Transplantation. 2009 Jan 27;87(2):198-206.
