ROLE OF INNATE IMMUNE RECEPTORS IN THE TYPE 1 DIABETES PATHOGENESIS

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SÃO PAULO
WHO projects that diabetes will be the 7th leading cause of death in 2030 (Global status report on noncommunicable diseases 2010. Geneva, World Health Organization, 2011).
What does the type 1 diabetes scenario look like nowadays?

Type 1 diabetes: translating mechanistic observations into effective clinical outcomes

Kevan C. Herold¹, Dario A. A. Vignali², Anne Cooke³ and Jeffrey A. Bluestone⁴

Unresolved areas of translational investigation

Although there has been much learned about the pathogenesis of T1D as a result of preclinical and clinical studies, several key questions have arisen and remain unanswered. Among these include:

What are the initiating factors?

Are viruses involved?

Are these unique or common? Are any of these factors intrinsic to β cells in T1D patients?

Which antigens are presented and does this change over time or in different patients?

How does the microbiome affect the induction or progression of autoimmunity?

How are innate responses involved?

What is the role of epigenetic changes in the penetrance of disease?
Diet, Microbiota and Immune System in T1D Development and Evolution

Mejía-León, M.E. et al., Nutrients, vol. 7, 2015
Interplay between innate and adaptive immunity

PRR: pattern recognition receptors
PAMPs: pathogen associated molecular patterns
DAMPs: damage associated molecular patterns

Tai, N et al., Journal of Autoimmunity, 1-9, 2016
NOD2 receptor activation confers susceptibility to STZ-induced T1D development

**A**  
STZ injections (40mg/kg/day)  
d0 d1 d2 d3 d4  
Sacrifice  
d7 d15  

**Multiple low doses (MLD-STZ)**

**B**  
Relative Expression  
Rip2  
Days after STZ treatment  
0 7 15  

**C**  
Relative Expression  
Nod1  
Days after STZ treatment  
0 7 15  

**D**  
Relative expression  
Ncd2  
Days after STZ treatment  
0 7 15  

**E**  
Relative Expression  
Rip2  
NOR NOD  

**F**  
Relative Expression  
Nod1  
NOR NOD  

**G**  
Relative Expression  
Nod2  
NOR NOD  

**H**  
Blood Glucose (mg/dL)  
Vehicle  
STZ  

**STZ** is a toxin that induces β-cell damage  
**NOD**: non-obese diabetic mice

*Costa et al, Accepted in J Exp Medicine*
NOD2 receptor activation confers susceptibility to STZ-induced T1D development

Costa et al, Accepted in J Exp Medicine
NOD2 receptor activation in DCs and macrophages induces a proinflammatory immune response in STZ-induced T1D.
NOD2 receptor activation is involved in the generation of Th1 and Th17 cells in vivo in STZ-induced T1D

Costa et al, Accepted in J Exp Medicine
Gut microbiota translocation to the pancreatic lymph nodes is implicated in T1D development

Costa et al, Accepted in, J Exp Medicine
NOD2 activation is sufficient to reestablish diabetes in diabetes resistant Abx-treated STZ-injected WT mice.

Costa et al, Accepted in, J Exp Medicine
NLRP3 and type 1 diabetes

Research Article
Two SNPs in NLRP3 gene are involved in the predisposition to type-1 diabetes and celiac disease in a pediatric population from northeast Brazil

ORIGINAL ARTICLE
A coding polymorphism in NALP1 confers risk for autoimmune Addison’s disease and type 1 diabetes

NF Magitta¹,²,³, AS Bøe Wolff¹,⁴,⁵, S Johansson¹,²,⁶, B Skinningsrud⁷,⁸, BA Lie⁹, K-M Myhr²,¹⁰, DE Undlien⁷,⁸, G Joner¹¹,¹², PR Njølstad²,¹³, TK Kvien¹⁴, Ø Førre¹⁵, PM Knappskog¹,²,¹⁶ and ES Husebye⁴,⁵,¹⁶
Diabetic mice have upregulation of NLRP3 inflammasome gene expression and IL-1β production in PLNs and pancreas

Carlos et al, Submitted to Frontiers Immunol
NLRP3 activation is required for insulitis and development of STZ-induced T1D

Carlos et al, Submitted to Frontiers Immunol
NLRP3 activation increases Th17/Tc17 and decreases the MDSC populations during T1D.

MDSC: myeloid-derived suppressor cells

Carlos et al, Submitted to Frontiers Immunol
Mitochondrial DNA triggers caspase-1-dependent IL-1β production by macrophages

A

BMDM: bone marrow-derived macrophages

Carlos et al, Submitted to Frontiers Immunol
Mitochondrial DNA from diabetic mice precipitates STZ-induced T1D onset

STZ: 4 sub-diabetogenic doses (40mg/Kg)
mDNA: Mitochondrial DNA (3 doses of 5 µg i.p. at days 0, 6 and 0 after STZ)
CONCLUSION

**PRR:** pattern recognition receptors

**PAMPs:** pathogen associated molecular patterns

**DAMPs:** damage associated molecular patterns
1) Young Investigator Project
Process Number: 2012/10395-0

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