ROLE OF INNATE IMMUNE RECEPTORS IN THE TYPE 1 DIABETES PATHOGENESIS

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FAPESP/EU-LIFE SYMPOSIUM on Cancer Genomics, Inflammation and Immunity

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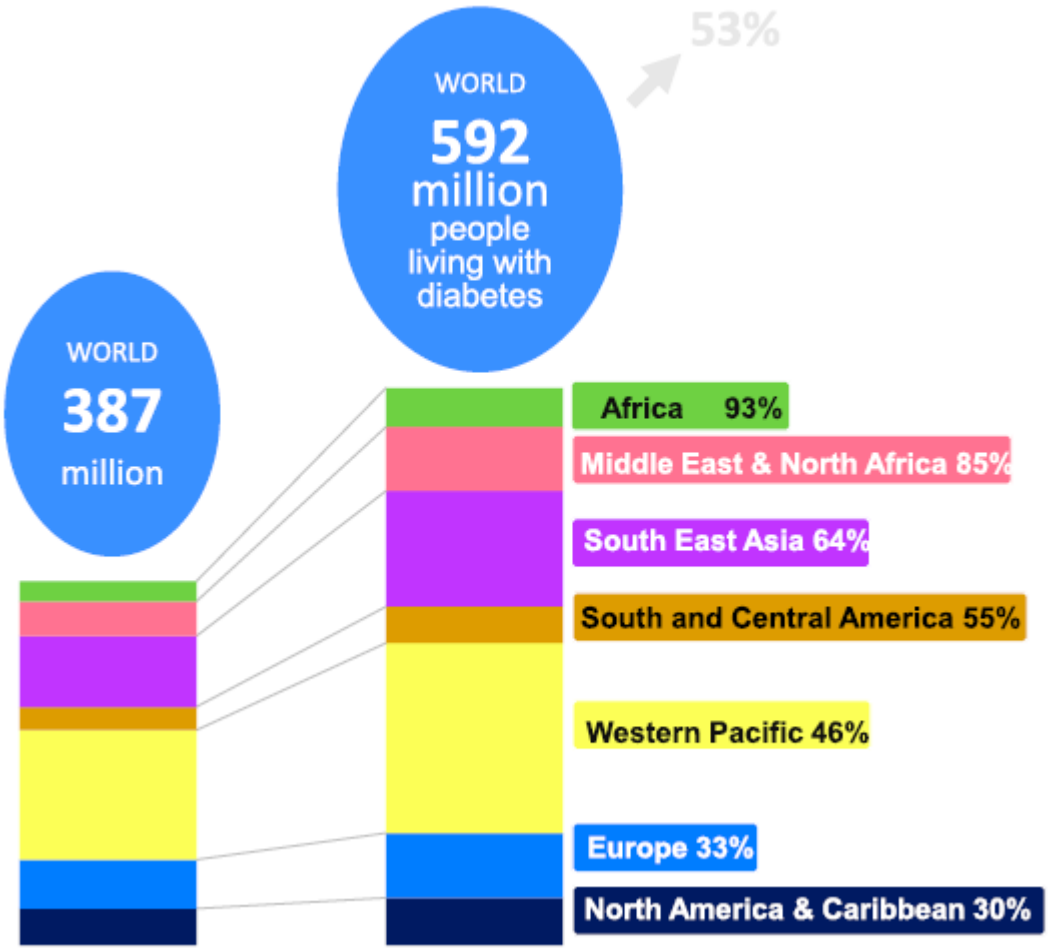
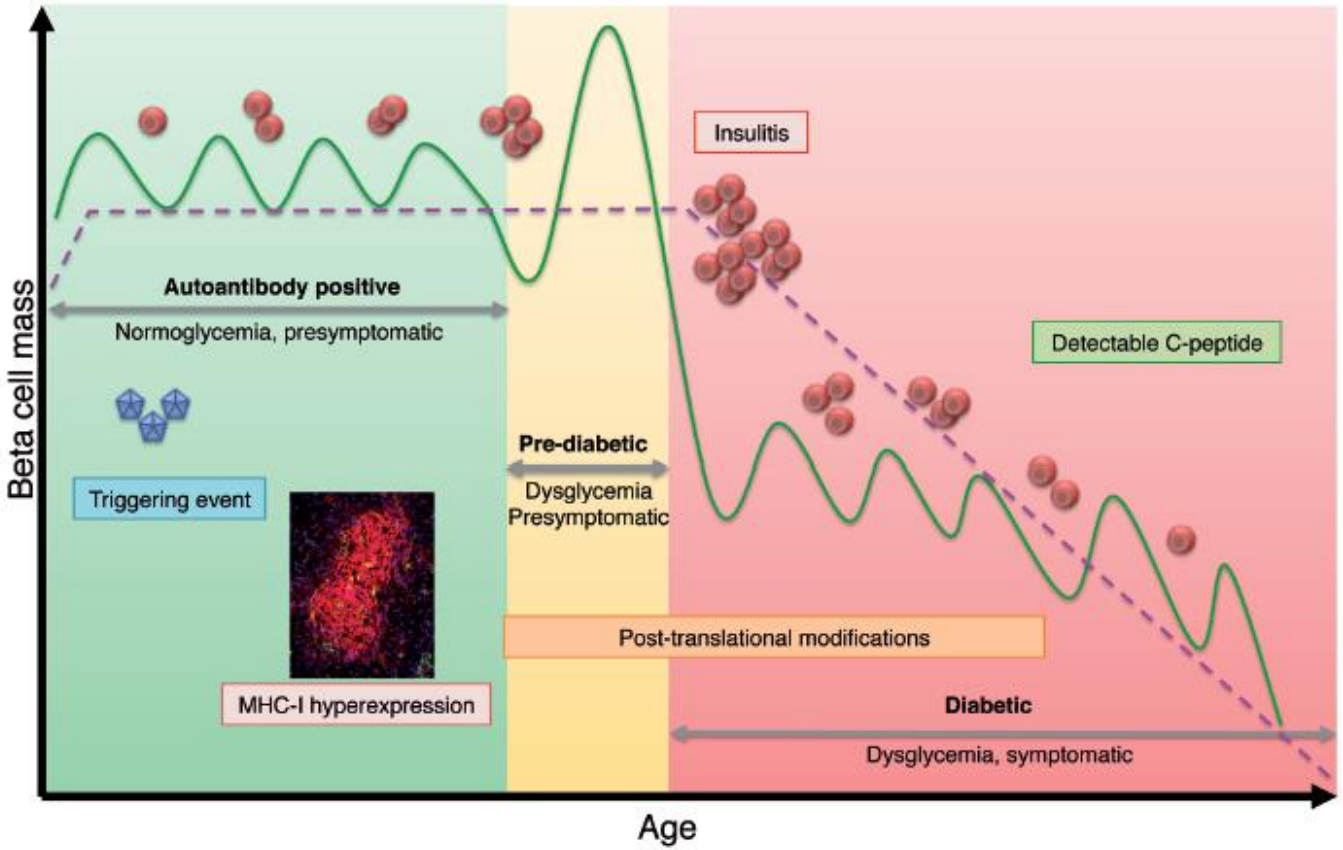
SÃO PAULO

Diabetes prevalence on the worldwide



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?



Christoffersson, G et al, F1000 Res, 2016

Type 1 diabetes: translating mechanistic observations into effective clinical outcomes

Kevan C. Herold[1], Dario A. A. Vignali[2], Anne Cooke[3] and Jeffrey A. Bluestone[4]

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 intrinic to β cells in T1D patients?

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

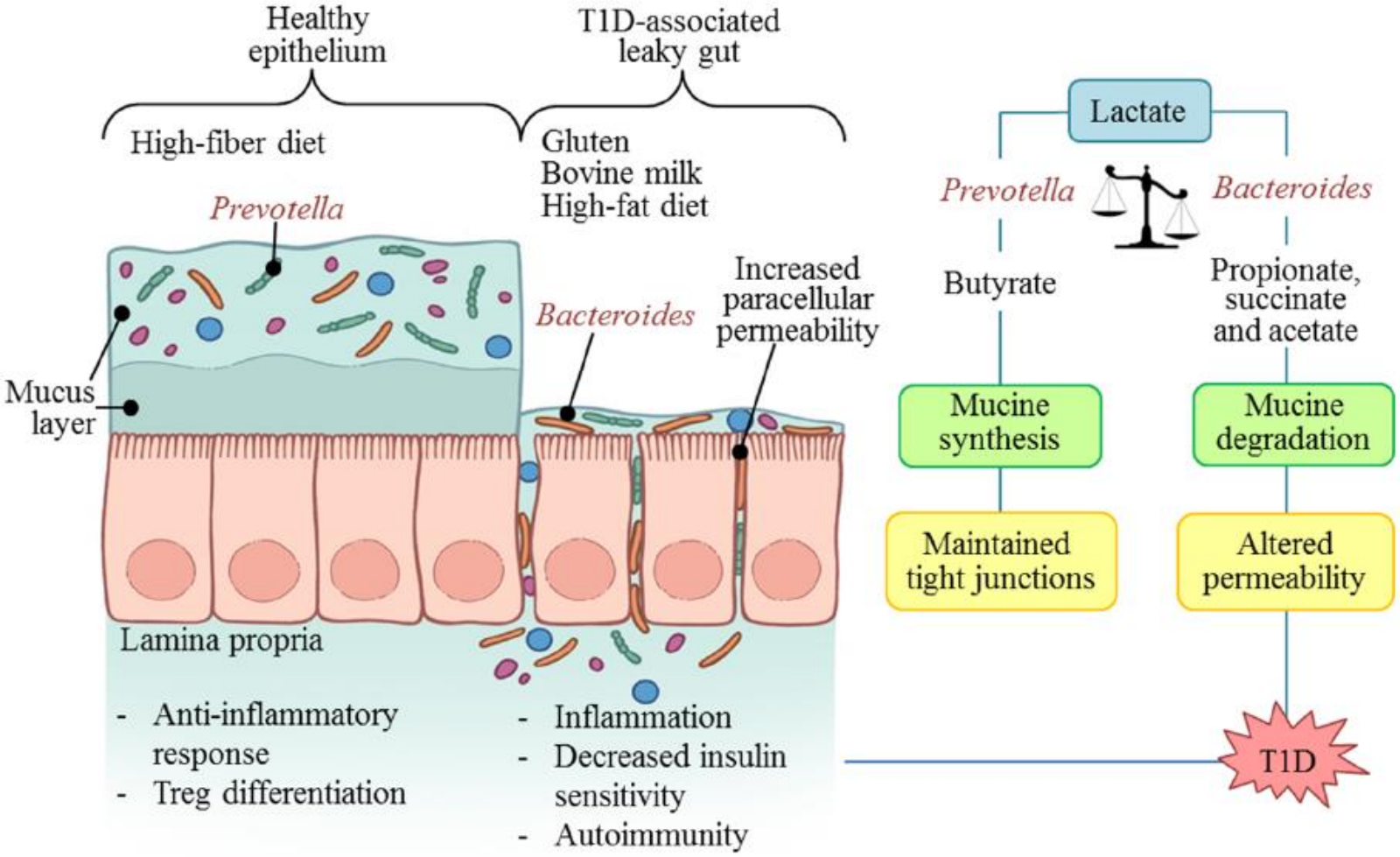
How does the microbiome affect the induction or progression of autoimmunity?

How are innate responses involved?

What is the role of epigenetic changes in the penetrance of disease?

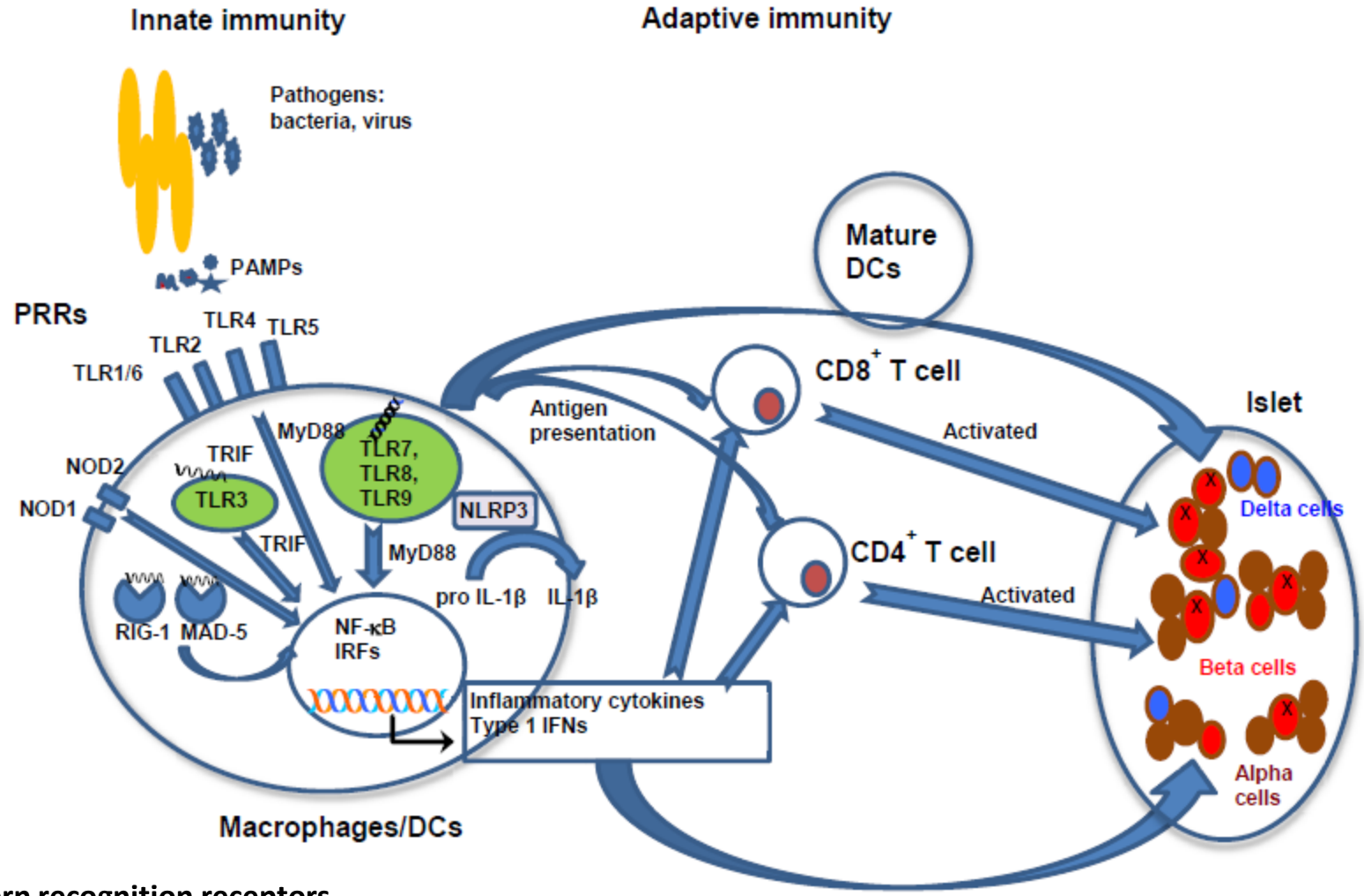
Herold, K.C et al, Nat Rev Immunolvol. 13(4), 2013

Diet, Microbiota and Immune System in T1D Development and Evolution



Mejía-León, M.E. et al., Nutrients, vol. 7, 2015

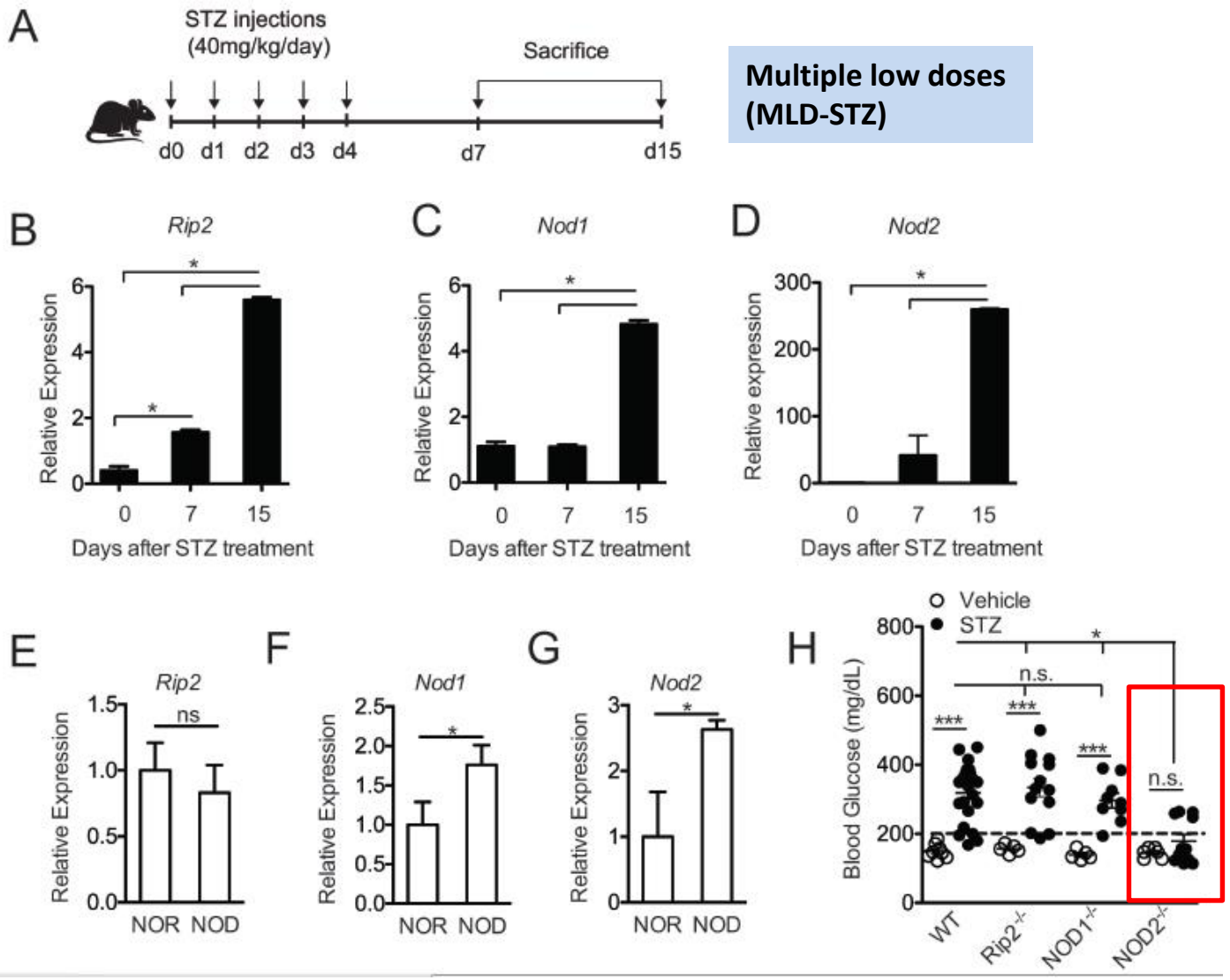
Interplay between innate and adaptive immunity



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

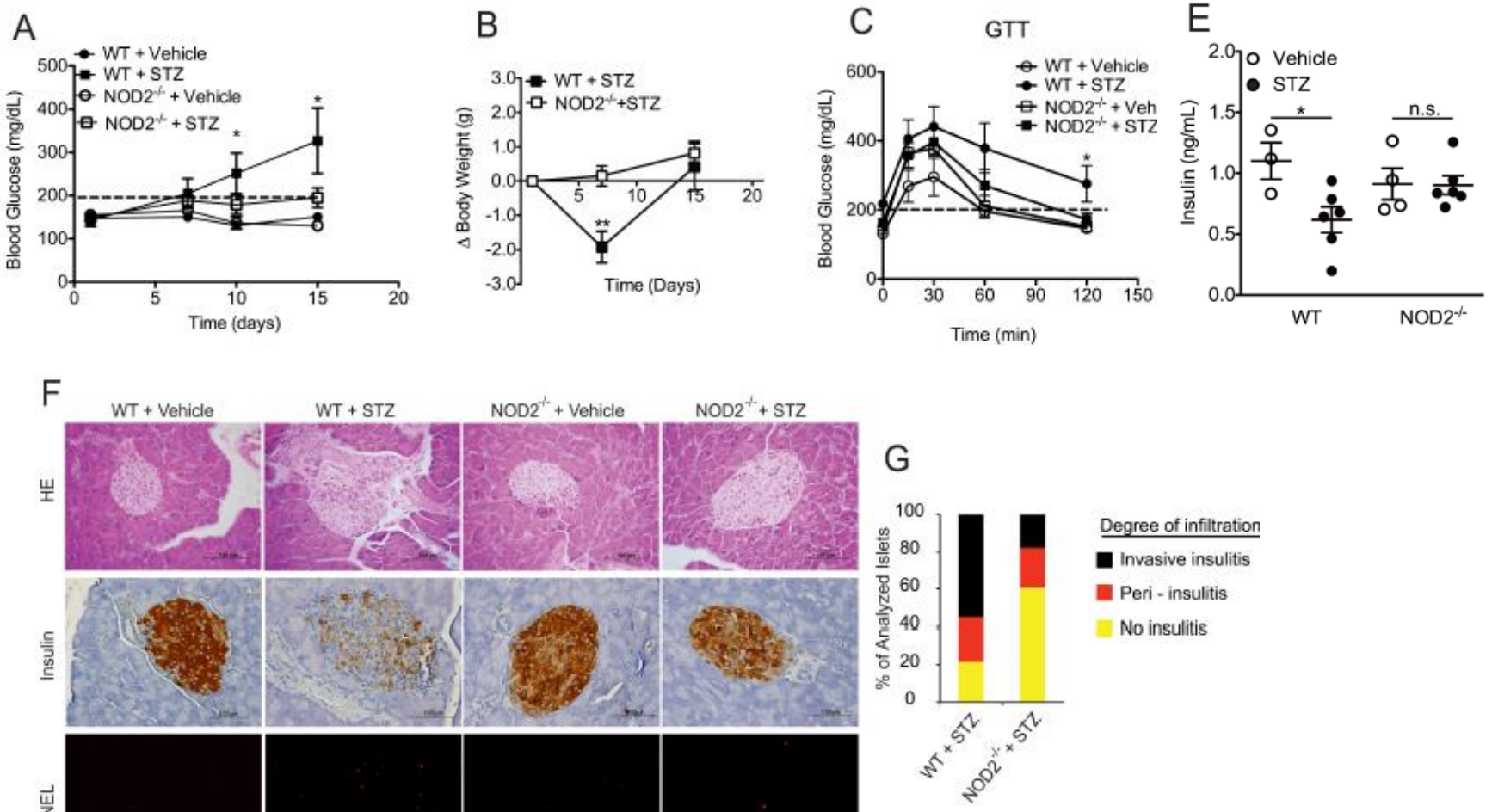


STZ is a toxin that induces β-cell damage

NOD: non-obese diabetic mice

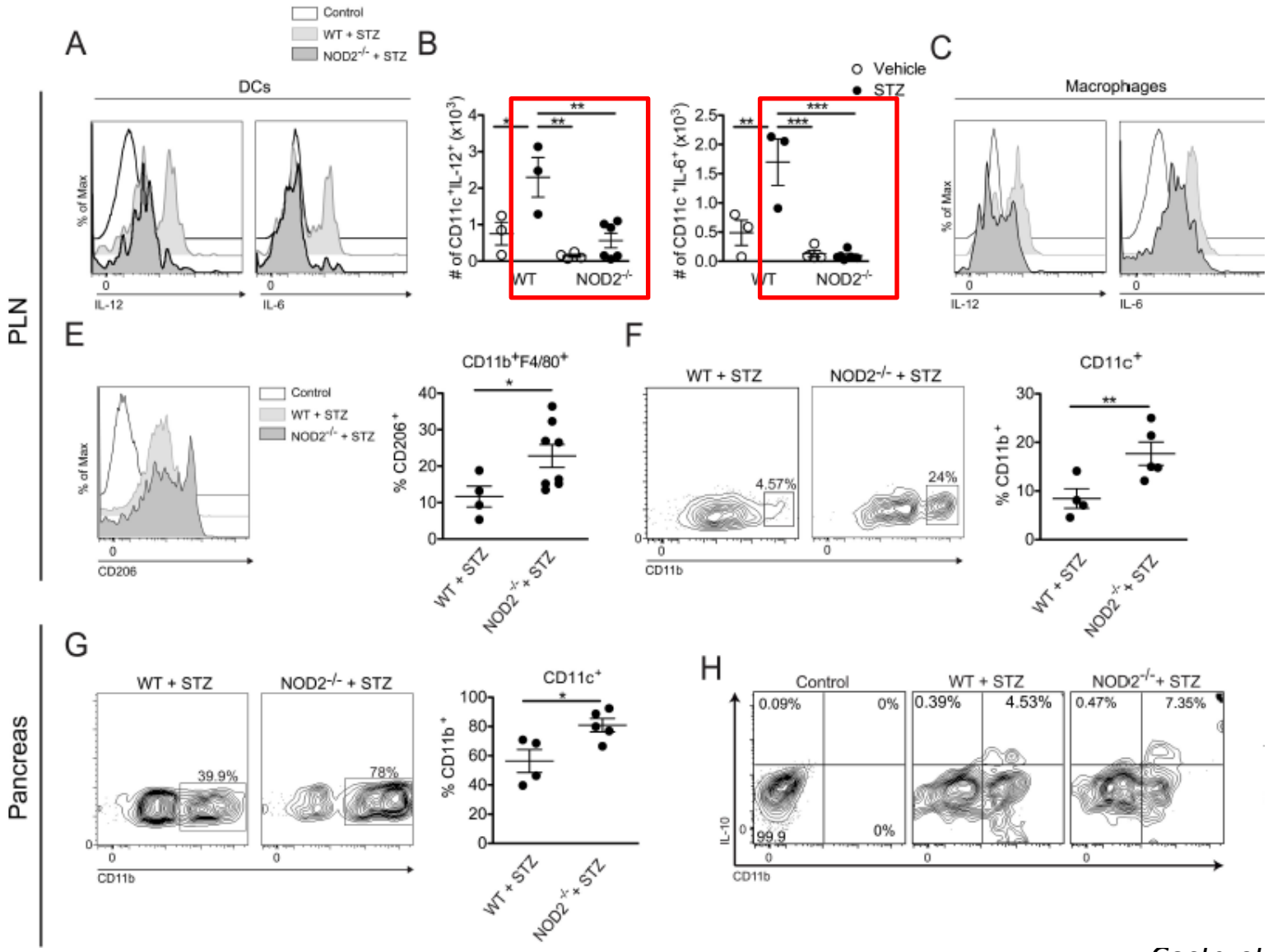
Costa et al, Accepted in J Exp Medicine

NOD2 receptor activation confers susceptibility to STZ-induced T1D development



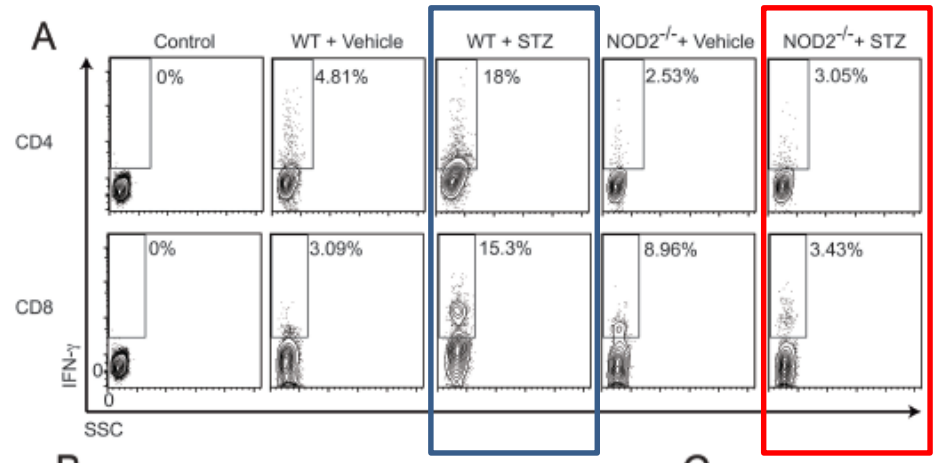
Costa et al, Accepted in J Exp Medicine

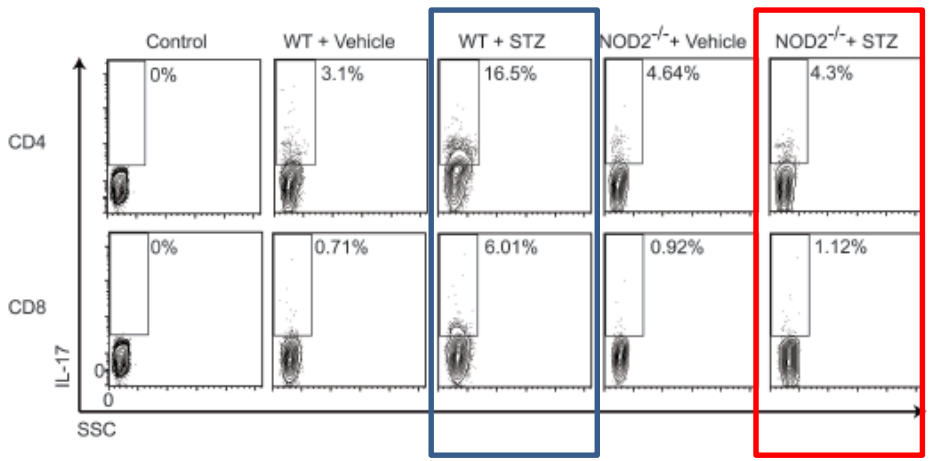
NOD2 receptor activation 247 in DCs and macrophages induces a proinflammatory immune response in STZ-induced T1D

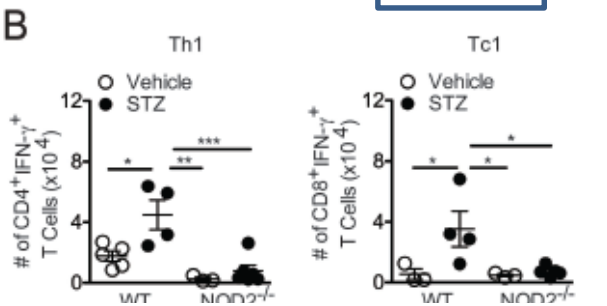


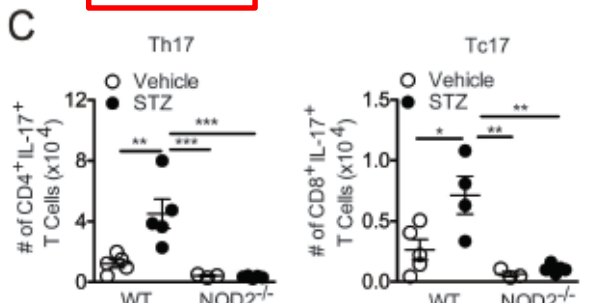
Costa et al, Accepted in J Exp Medicine

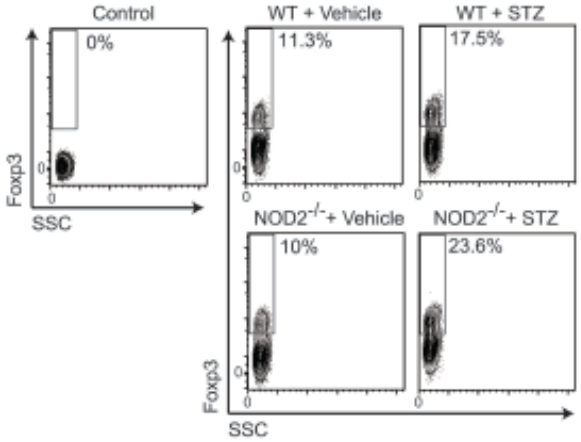
NOD2 receptor activation is involved in the generation of Th1 and Th17 cells in vivo in STZ-induced T1D

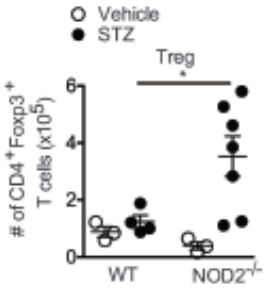


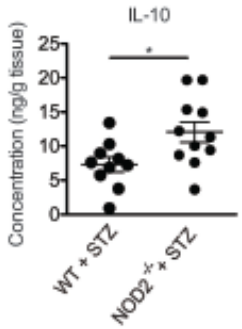






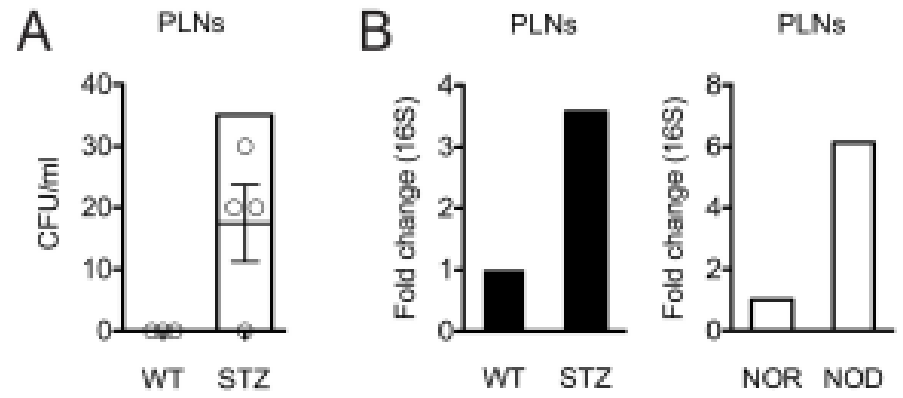


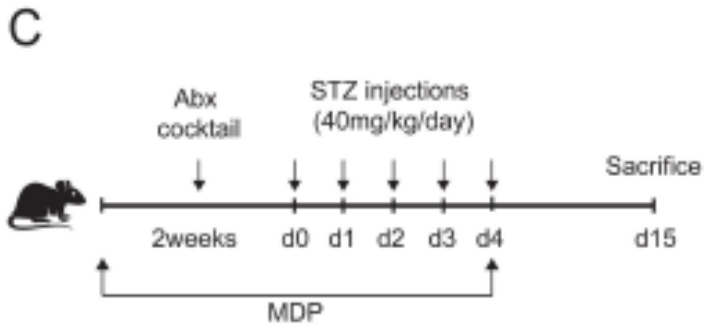


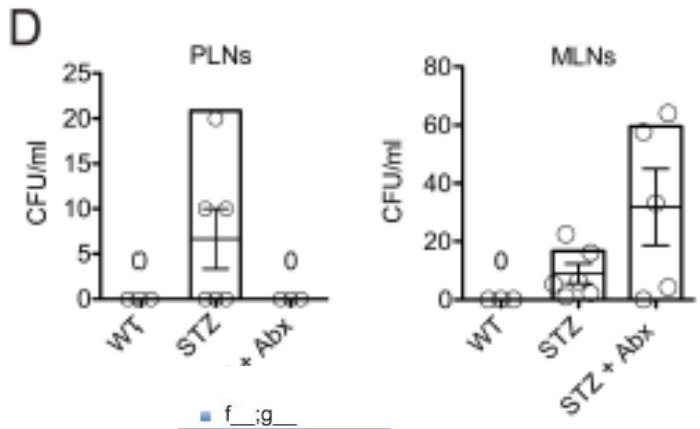


Costa et al, Accepted in J Exp Medicine

Gut microbiota translocation to the pancreatic lymph nodes is implicated in T1D development

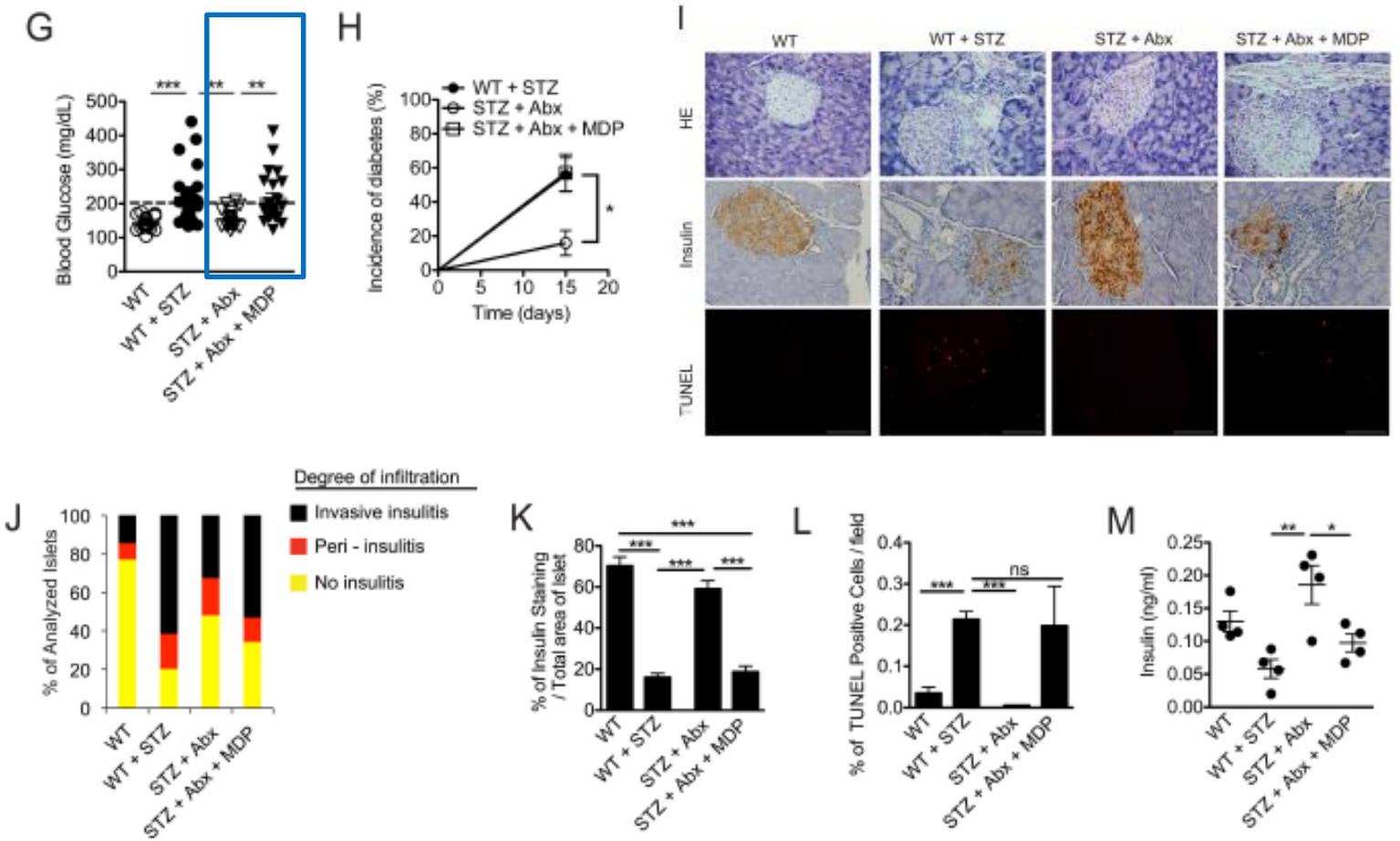






Costa et al, Accepted in, J Exp Medicine

NOD2 activation is sufficient to reestablish diabetes in diabetes resistant Abx-treated STZ-injected WT mice.



Costa et al, Accepted in, J Exp Medicine

NLR and type 1 diabetes

Research Article

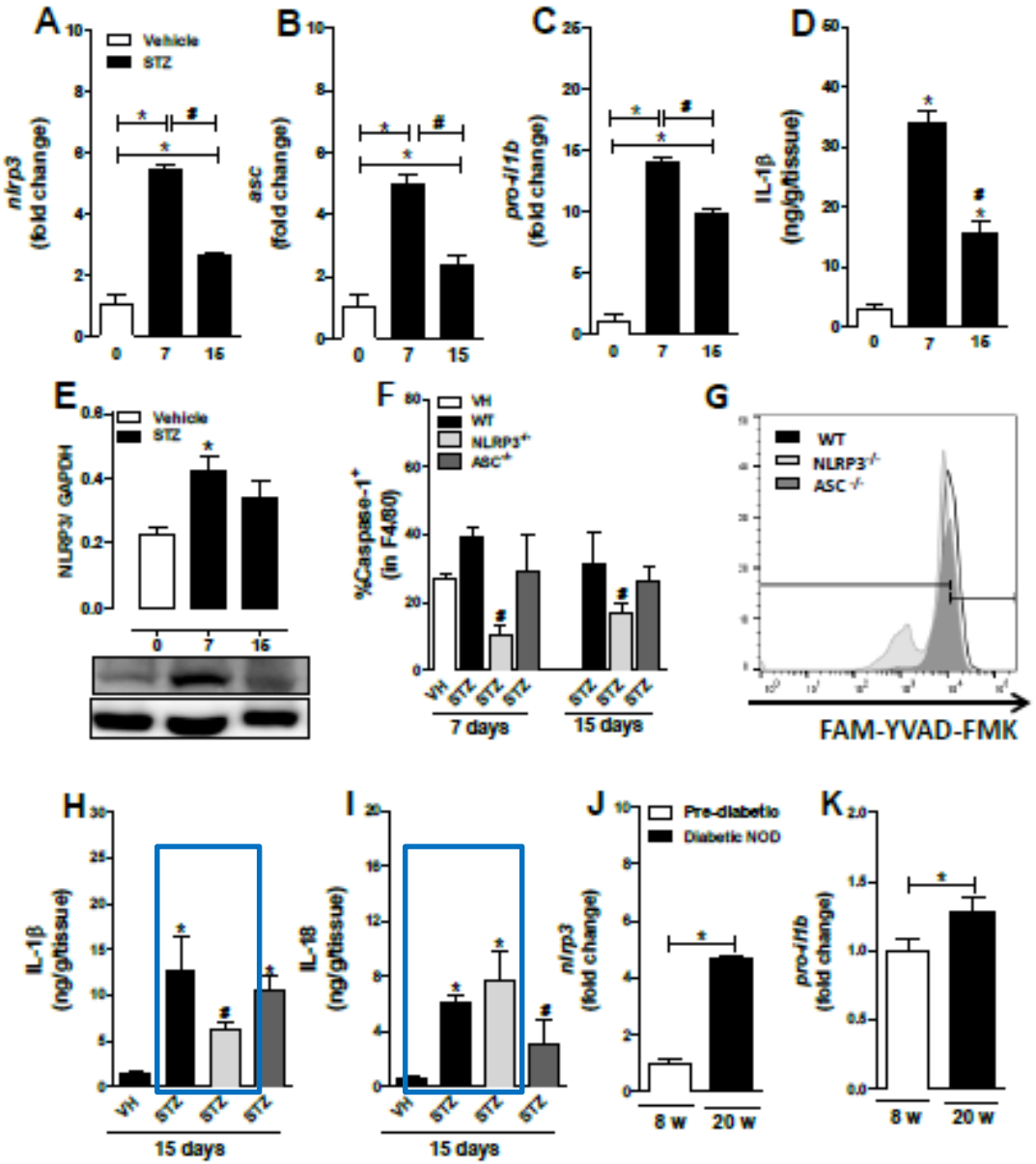
Two SNPs in *NLRP3* gene are involved in the predisposition to type-1 diabetes and celiac disease in a pediatric population from northeast Brazil

ORIGINAL ARTICLE

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

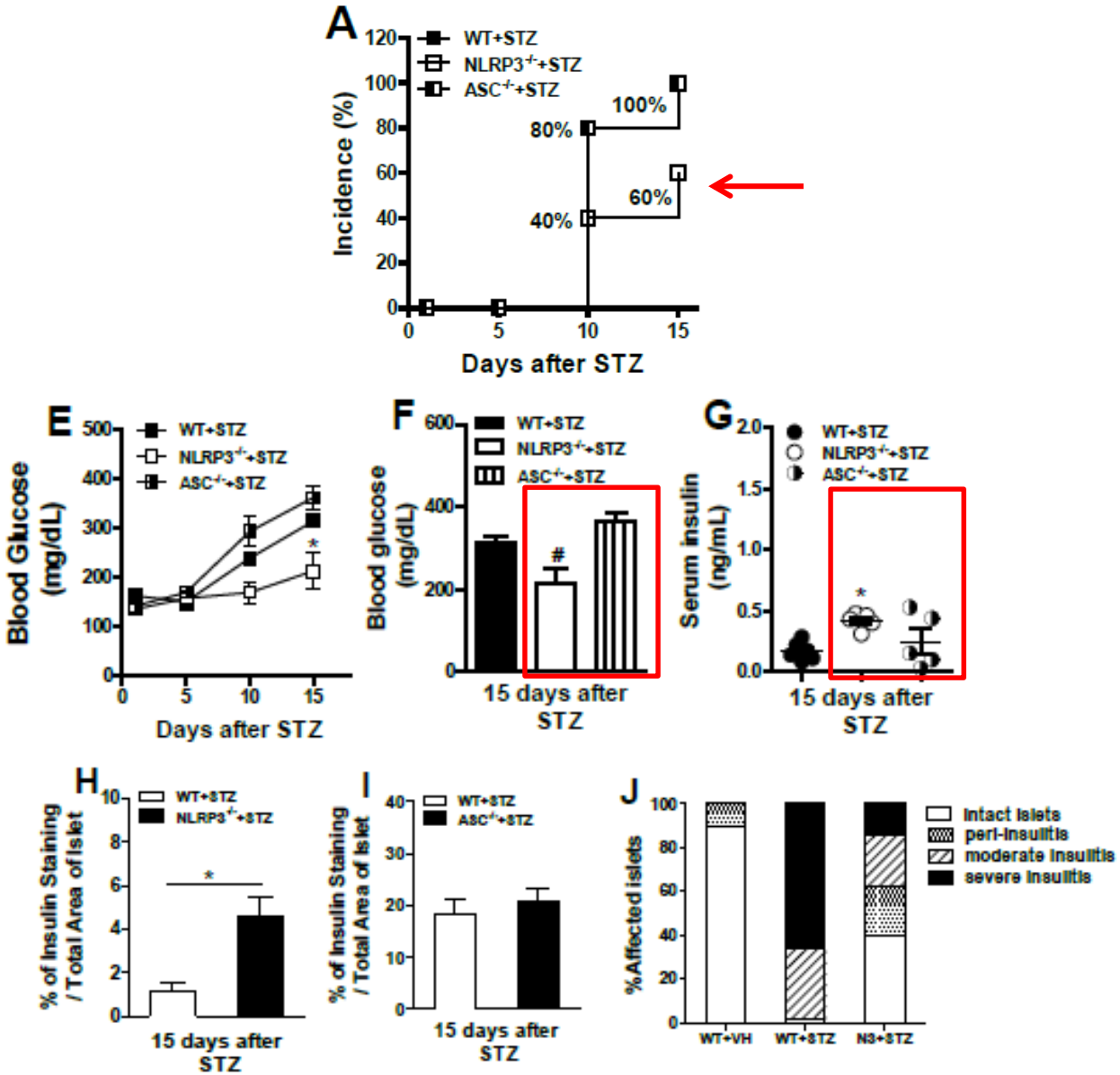
NF Magitta[1,2,3], AS Bøe Wolff[1,4,5], S Johansson[1,2,6], B Skinningsrud[7,8], BA Lie[9], K-M Myhr[2,10], DE Undlien[7,8], G Joner[11,12], PR Njølstad[2,13], TK Kvien[14], Ø Førre[15], PM Knappskog[1,2,16] and ES Husebye[4,5,16]

Diabetic mice have upregulation of NLRP3 inflammasome gene expression and IL-1β production in PLNs and pancreas



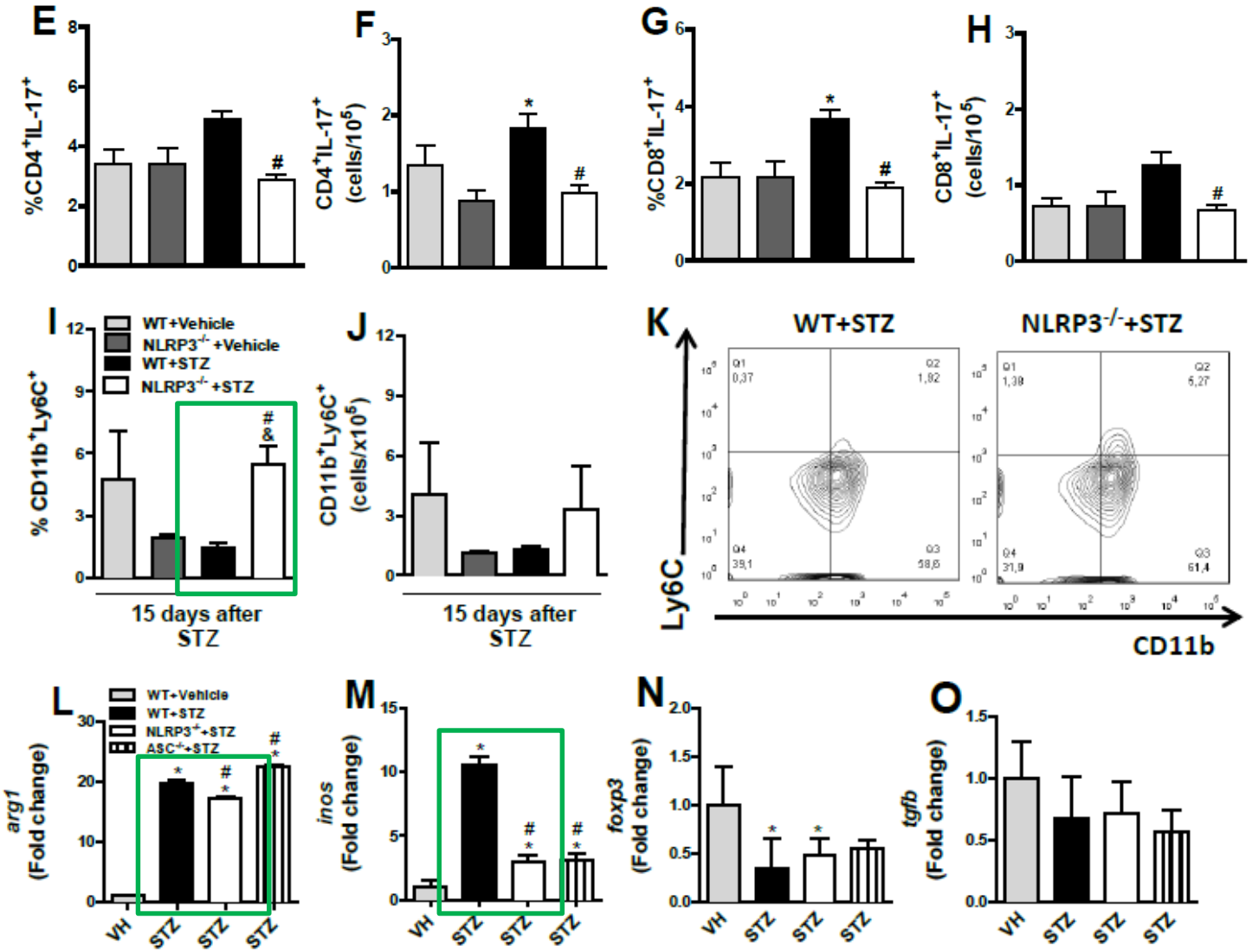
Carlos et al, Submitted to Frontiers Immunol

NLRP3 activation is required for insulitis and development of STZ-induced T1D



Carlos et al, Submitted to Frontiers Immunol

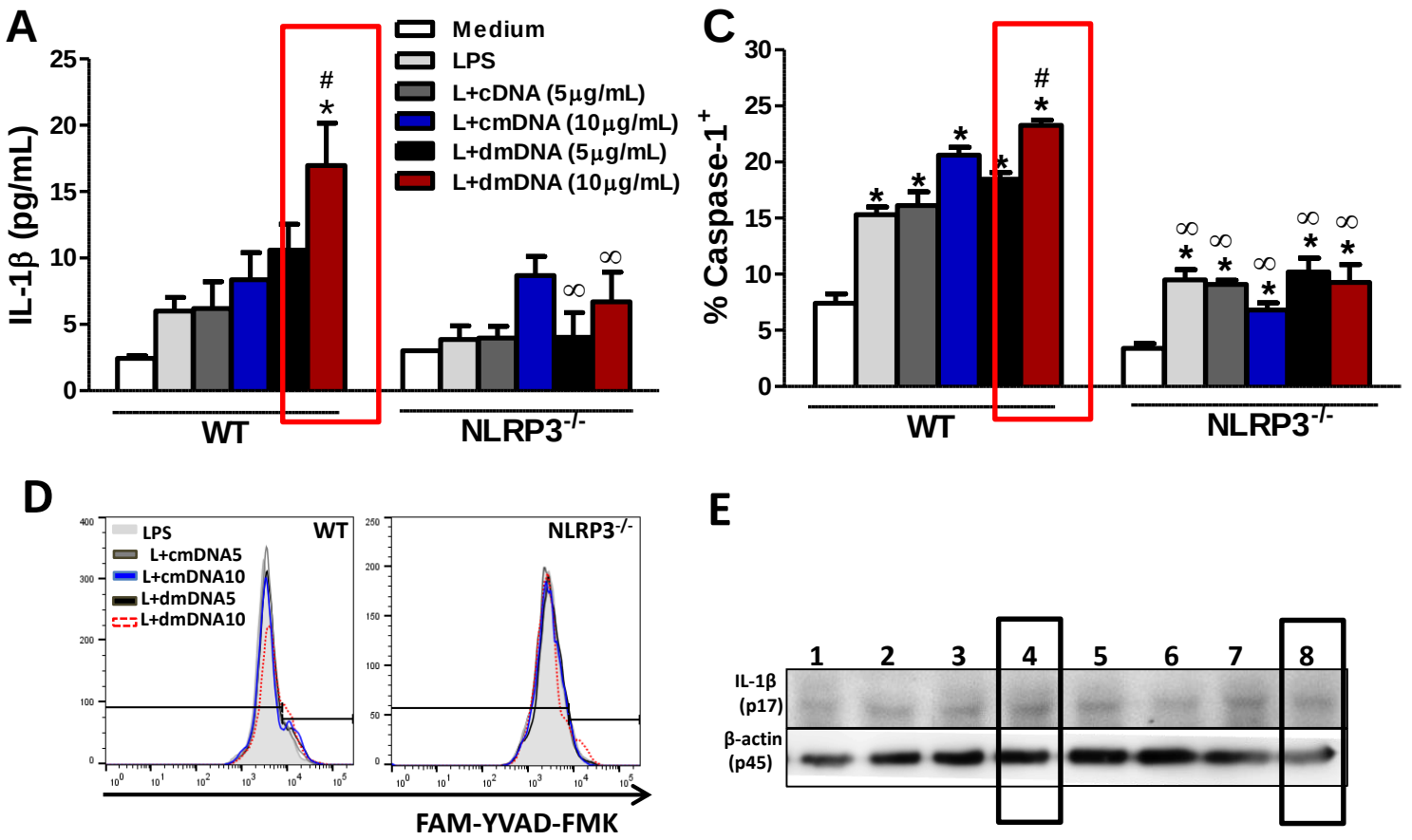
NLRP3 activation increases Th17/Tc17 and decreases the MDSC populations during T1D



MDSC: **myeloid-derived supressor cells**

Carlos et al, Submitted to Frontiers Immunol

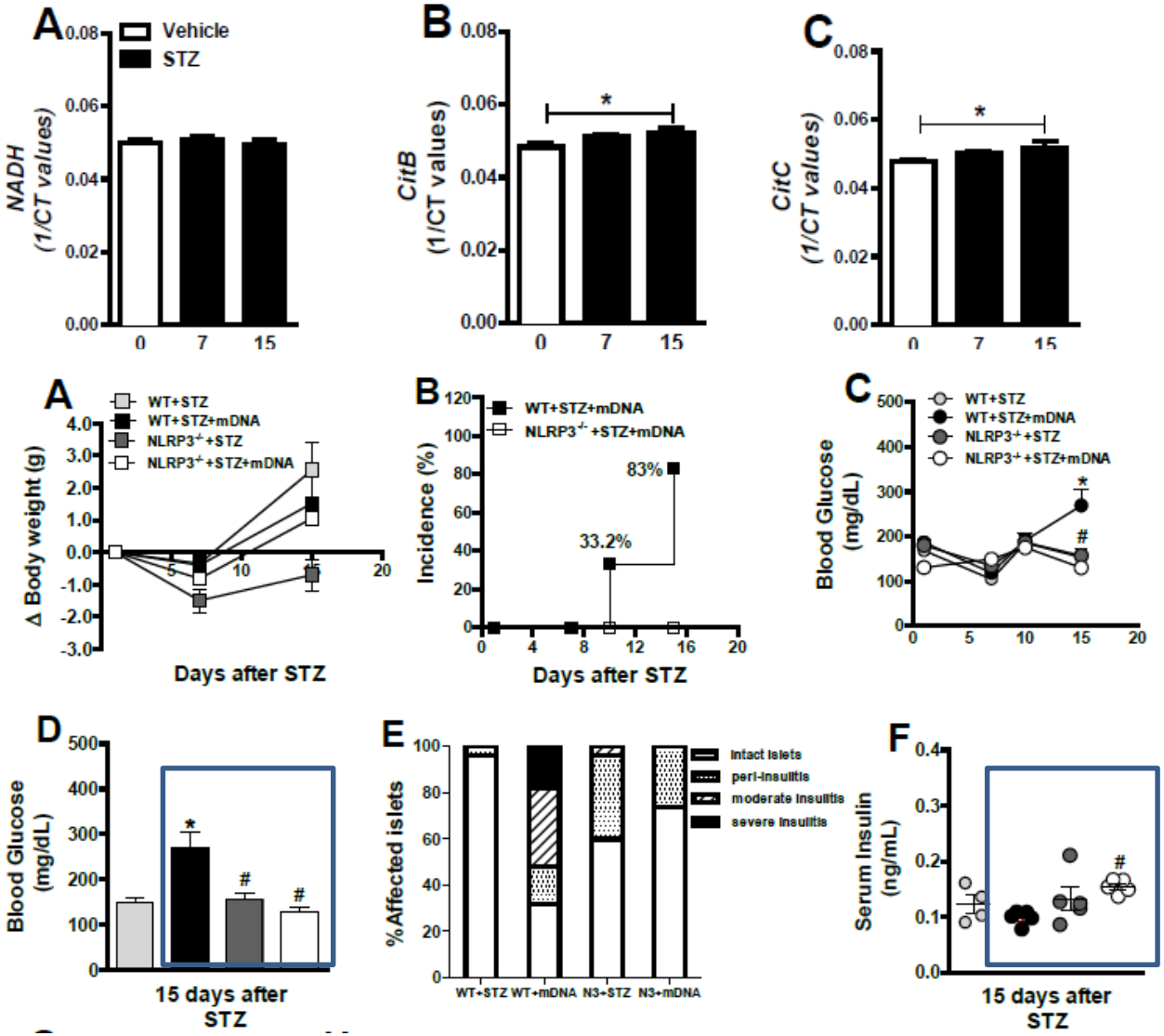
Mitochondrial DNA triggers caspase-1-dependent IL-1β production by macrophages



BMDM: bone marrow-derived macrophages

Carlos et al, Submitted to Frontiers Immunol

Mitochondrial DNA from diabetic mice precipitates STZ-induced T1D onset

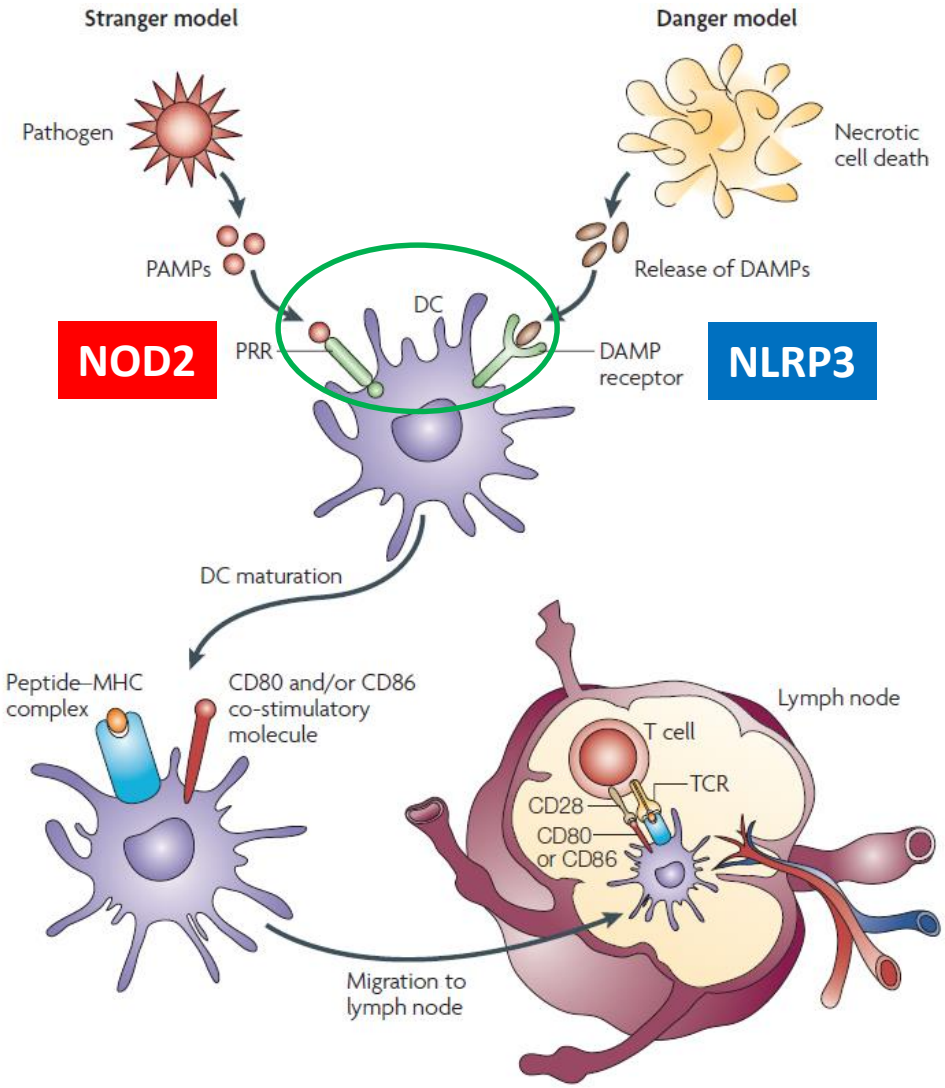


STZ: **4 sub-diabetogenic doses (40mg/Kg)**

mDNA: Mitochondrial DNA (3 doses of 5 µg i.p. at days 0, 6 and 0 after STZ)

Carlos et al, Submitted to Frontiers Immunol

CONCLUSION



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

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