Novel molecular mechanisms regulating autoimmune T cell functions

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Type 1 diabetes is an autoimmune disease associated with hyperglycemia and chronic inflammation that leads to several secondary complications. We found that hyperglycemia induces O-GlcNAcylation the NF-kappaB protein c-Rel at a single serine residue, S350. c-Rel plays a critical role in controlling regulating T cell function and T regulatory cell development. O- GlcNAcylation of c-Rel at S350 enhances the transcription of c-Rel-induced CD28RE- dependent pro-autoimmune cytokines, interleukin-2 (IL-2), interferon gamma (IFNG) and granulocyte macrophage colony stimulating factor (GM-CSF). We also found that the regulatory effect of c-Rel O-GlcNAcylation is gene dependent and it suppresses the transcription of forkhead box P3 (FOXP3) expression in T cells. Together, these data suggest that c-Rel O- GlcNAcylation has a novel, dual regulatory role in controlling T cell function by enhancing pro- autoimmune T cell function and suppressing Treg function. This creates an immune environment that may exacerbate the progress of autoimmunity. Mechanistically, we found that O-GlcNAcylation enhances the DNA binding of c-Rel at CD28RE and decreases it's binding at the FOXP3 promoter. This study reveals a novel molecular mechanism that regulates NF- kappaB c-Rel and autoimmune diabetes, with potential to develop novel therapeutics targeting c-Rel O-GlcNAcylation. Moreover, this study serves as the basis to explore the role of c-Rel O- GlcNAcylation in other autoimmune diseases such as celiac disease, lupus and arthritis, where c-Rel function have been implicated.

Biography

Param Ramakrishnan has completed his PhD from Weizmann Institute of Science, Israel and postdoctoral studies from California Institute of Technology, USA under the mentoring of Nobel Laureate Dr. David Baltimore. Currently, he is a tenure track assistant professor, at Case Western Reserve University, Cleveland Ohio, with secondary appointment at Cleveland Clinic Foundation. He has published more than 25 papers in reputed journals, hold 12 international patents and has been serving as an editorial board member of repute in 7 international journals.

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