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17TH GLOBAL DIABETES CONFERENCE & NURSING CARE

March 08-09, 2018 | Paris, France

# Transcriptional control of inflammation as an innate immune sensor of metabolic stress in diabetes

**Fawaz Alzaid[1], T Ejlalmanesh[1], J B Julla[1], L Orliaguet[1], M Kondili[1], M Mathew[1], R Ballaire[1], C Chollet[1], J P Riveline[1], V Paradis[2], I Udalova[3], J F Gautier[1]** and **N Venteclef[1]**

[1]Sorbonne Universités-Université Pierre et Marie-Curie, France
[2]Beaujon Hospital, Assistance Publique-Hopitaux de Paris, France
[3]University of Oxford, UK

In type-2 diabetes, sterile inflammation efferent from innate immunity is causal in the onset of insulin resistance and progression of complications and comorbidities. However, the precise metabolic stressors and their processing by innate immune cells remain elusive. Our aim is to determine which metabolic factors are immunogenic and to decipher the cellular metabolic pathways that integrate such signals and lead to an Inflammatory activation. We recently demonstrated that the type-1 interferon response underlies diabetogenic, genetic deletion of its mediator, interferon regulatory factor (Irf)-5, rescues mice from insulin resistance and steatohepatitis. Unexpectedly, the Irf5-deficient transcriptome in macrophages was characterized by up-regulation of pathways governing cellular lipid metabolism. In this capacity, we propose that Irf5 and its dependent transcripts, act as metabolic sensors, relaying glucolipotoxicity and mediating adaptive cellular metabolism for effective inflammatory activation. To address this we have carried out in-depth analysis of the macrophage cellular energetic and metabolic environment in response to metabolic stressors under Irf5-competence and Irf5-deficiency. We observed that indeed Irf5 and its inflammatory targets are responsive to specific metabolic stimuli. In a human study we analyzed Irf5 expression in circulating innate immune cells to determine the prognostic value of innate immunity's sensitivity to metabolic cues. We observed that Irf5 expression is responsive in circulating cells from type-2 diabetic patients and is associated with specific serological parameters relating to dyslipidemia. Interestingly, Irf5 in monocyte and dendritic cell subtypes is specifically regulated in the presence of vascular and hepatic complications of long-standing diabetes. These data suggest that initiation of the type-1 interferon response is extremely sensitive to metabolic status and may be predictive of disease progression or susceptibility to diabetic complications. Further studies will delineate the pathways linking metabolic cues to activation of Irf5, developing novel immunotherapeutic targets in diabetes.

## Biography

Fawaz Alzaid is a Research Associate of the French National Institute of Health and Medical Research (INSERM). His recent research highlights include first author publications in Nature Medicine and JCI Insight deciphering mechanisms of tissue inflammation in diabetes.

fawaz.alzaid@gmail.com

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