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Rapid induction of IFN-beta in primary human monocytes mediated by monocyte-specific regulators

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Robust and rapid induction of interferon- β (IFN- β) in monocytes following pathogenic stimulation is a hallmark of innate immune responses. Here, we reveal the molecular mechanism underlying this key property that is exclusive to human blood monocytes. We found that IFN- β is produced rapidly in primary human monocytes as a result of co-operation between the myeloid-specific transcription factor *IRF8* and the ubiquitous transcription factor IRF3. Knock-down of IRF8 in monocytes abrogated IFN- β transcription, while reintroduction of IRF8 into the IRF8-/- 32Dcl3 murine myeloid cell line reinstated *IFN- β* transcription. Moreover, we provide evidence that IRF8 constitutively binds to the ETS/IRF composite element (EICE) of the *IFN- β* promoter region together with PU.1 *in vivo*. Furthermore we uncovered a requirement for IRF3, a master regulator of IFN- β production, as a previously unidentified interaction partner of IRF8. We mapped the protein-protein interacting regions of IRF3 and IRF8, and found that their interaction was independent of the DNA-binding domain (DBD) and the IRF association domain (IAD) of IRF8 and IRF3, respectively. Based on our data, we propose a model for the rapid induction of *IFN- β* in monocytes, whereby IRF8 and PU.1 form a scaffold complex on the *IFN- β* enhancer to facilitate the recruitment of IRF3, thus enabling rapid *IFN- β* transcription.

Biography

Keh-Chuang Chin graduated in Biochemistry from the University of Iowa in 1996 and obtained his D. Phil in Biochemistry and Biophysics at the University of North Carolina at Chapel Hill 1997, where he did his studies on the transcriptional regulation of class II major histocompatibility molecules (MHC-II) under the supervision of Dr. Jenny Ting. After post-doctoral work in Dr. Peter Cresswell's lab (Howard Hughes Medical Institute, Section of Immunobiology, Yale University), he was appointed as Senior Research Scientist at the Genome Institute of Singapore in 2003. He joined SigN in 2006.