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DEFENSE OF THE DOCTORAL

DISSERTATION

"Interplay between two DNA-sensing pathways in plasmacytoid dendritic cells and the role of toll-like receptor 10 in pDC biology"

by

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Molecular Biology, Genetics, & Cancer Track

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Thursday, May 23rd, 2019
10:00 A.M.
MSB Room No: B 610

ABSTRACT

Abstract: Plasmacytoid dendritic cells (pDCs) are potent producers of type-I and type-III interferons (IFNs) and play major roles in antiviral immunity and autoimmune disorders. pDCs recognize unique molecular signatures of invading pathogens called "pathogen-associated molecular patterns" (PAMPs) that trigger the downstream pathways leading to IFN production. The innate sensing of nucleic acids remains the major initiating factor for IFN production by pDCs. Certain receptors called "pattern recognition receptors" (PRRs) facilitate this recognition of PAMPs, including nucleic acids. Toll-like receptors (TLRs) remain the most well-known PRRs to date. TLR-9 is known as the sole innate sensor of DNA in the endosomal compartment of mammalian cells. Recently, a cytosolic DNA sensing pathway mediated by cGAMP synthetase (cGAS) and endoplasmic reticulum resident protein stimulator of interferon genes (STING) has been discovered. It has been documented that upon recognition of DNA in the cytosolic compartment, cGAS recruits adenosine triphosphate (ATP) and guanosine triphosphate (GTP) of the host cell and produce the cyclic dinucleotide cyclic 2′3′ cyclic AMP-GMP (cGAMP). cGAMP binds to STING to initiate the downstream pathway leading to cytokine production. Here, we have demonstrated the existence and functionality of the components of the cytosolic DNA sensing pathway comprising of cGAS and STING in human pDCs. Upon direct stimulation of pDCs by STING agonist cGAMP or double-stranded DNA (dsDNA), pDCs produced type-I and type-III interferon. Moreover, we documented that cGAS-STING-mediated IFN production is orchestrated by nuclear translocation of IRF3 while TLR9-mediated activation occurs through IRF7. Our data also indicate that pDC pre-stimulation of cGAS-STING dampened the TLR9-mediated IFN production possibly by an autoinhibitory loop involving the expression of suppressor of cytokine signaling 1 and 3 (SOCS1 and -3). Thus, our study demonstrates that the cGAS-STING pathway exists in parallel to the TLR9-mediated DNA recognition in human pDCs with crosstalk between these two pathways.

Toll-like receptors (TLRs) are the most thoroughly studied group of pattern-recognition receptors (PRRs) that play a central role in innate immunity. Among them, TLR10 remains the only TLR family member without a known ligand and clearly defined functions. Here, we have interrogated the expression and function of TLR10 in human pDCs. We have seen that primary human pDCs, B cells, and monocytes constitutively express TLR10. Upon pre-incubation with an anti-TLR10 antibody, production of cytokines in pDC was downregulated in response to stimulation with DNA and RNA viruses. Upon further investigation into the possible mechanism, we documented phosphorylation of signal transducer and activator of transcription 3 (STAT3) upon antibody-mediated engagement of TLR10 leading to induction of SOCS3. We have also documented the inhibition of nuclear translocation of transcription factor IFN regulatory factor 7 (IRF7) in pDCs following TLR10 engagement. Our data provide the first evidence that TLR10 is constitutively expressed on the surface of human pDCs and works as a regulator of their innate response. Our findings indicate the potential of harnessing the function of pDCs by antibody-mediated targeting of TLR10 that may open a new therapeutic avenue for autoimmune disorders.