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# POLA1 REGULATES TYPE I INTERFERON ACTIVATION THROUGH CYTOSOLIC RNA:DNA SYNTHESIS

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Cells detect viral infection mainly by sensing viral nucleic acids either in the endosomes during viral entry or in the cytosol during viral replication. Activation of any of these pathways leads to type I interferon responses, and mutations affecting genes involved in these sensing mechanisms can lead to altered immune responses. The study of such disorders has provided key insights into the molecular architecture of these pathways in humans.

In this study, we review our recent discovery that a hypomorphic mutation in *POLA1*, encoding the catalytic subunit of DNA polymerase-α, causes X-linked reticulate pignantary syndrom (MIM: 301220), characterized by recurrent infections and sterile inflammation in various organs. Pol-α, which exists in a stable complex with Primase, is responsible for initia ting Okazaki fragments synthesis during DNA replication. POLA1 deficiency in patient-derived cells or after siRNA mediated silencing, leads to overexpression of multiple interferon-stimulated genes (ISGs). Further investigation revealed that POLA1 is required for the synthesis of previously uncharacterized short cytoplasmic RNA:DNA hybrid molecules, which modulate activation of the type I interferon pathway. Finally, this activity was explained through introdiction of immunologically inert short RNA:DNA, which is dramatically decreased under POLA1 deficiency states. This material, when extracted from cells or made in synthetic fashion, can suppress ISG expression in response to activation of nucleic acid sensors.

In conclusion, the current model of intracellular immune response may be augmented by a new player. In addition to its nuclear functions, POLA1 generates im-munomodulatory RNA:DNA hybrids. These molecules could function to set a higher activation threshold for nucleic acid receptors, preventing cells from spontaneous activation by DNA or RNA molecules generated during normal cell processes. Finally, we believe that imbalances in the normal regulation of this pathway are associated with the immune dysfunction in XLPDR, and probably may be involved in the pathophysiology of other immune disorders.

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