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Replication protein lysine acetylation regulates the fidelity of the human genome

Lata Balakrishnan, Onyeka Ononye, and **Catherine Njeri**
Indiana University Purdue University Indianapolis, USA

The process of DNA replication needs to occur with extremely high accuracy and efficiency. Mutations incorporated into the genetic code can cause downstream errors in the creation of proteins, which carry out functional activities within the cell. This in turn directly impacts human health, promoting oncogenesis and faster progression to cancer. In eukaryotic nuclear DNA replication, the leading strand is synthesized continuously, but the lagging strand must be made as short Okazaki fragments that are later joined. Maturation of the lagging strand is an inherently complex process involving multiple enzymes. We have found many proteins associated with DNA replication and/or repair to be post-translationally modified by lysine acetylation. Nick translation allows for the displacement of short flaps, followed by cleavage by FEN1 and subsequent ligation. The nuclease activity of FEN1 is diminished on lysine acetylation. In contrast, acetylation of DNA polymerase delta and Pif1 create longer flaps in the cell, owing to an increase in strand displacement synthesis and helicase function respectively. The acetylated form of RPA binds these displaced flaps with high affinity. Stimulated nuclease function of acetylated DNA2 allows for efficient processing of the flaps for ligation. Similarly, acetylation of many proteins in the base excision repair pathway promotes the displacement of a longer patch of damaged bases. Additionally, we found that in human cells repair efficiency was diminished in the absence of acetylation. The displacement of longer flaps would ensure the removal of mismatched bases synthesized by the error-prone DNA polymerase alpha during the maturation phase and damaged nucleotides during the repair process. We propose that lysine acetylation of these proteins acts as a regulatory mechanism that ensures the optimal functioning of the replication/repair-associated proteins in a manner that is consistent with promoting genome stability.

Biography

Lata Balakrishnan is an Assistant Professor in the Department of Biology in the School of Science at Indiana University Purdue University Indianapolis. The current research in the Balakrishnan laboratory is focused on understanding the mechanistic reactions of eukaryotic lagging strand DNA synthesis, and the accompanying DNA repair processes. She trained with Dr Robert Bambara, at the University of Rochester for her post-doctoral fellowship and received her PhD under the mentorship of Dr Barry Milavetz at University of North Dakota, wherein her dissertation work defined the epigenetic code during viral transcription.

latabala@iupui.edu

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