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Mechanism of action of Hdac1,2 selective inhibitors on DNA replication– therapeutic implications in cancer therapy

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Histone deacetylases 1 and 2 (Hdacs1,2) localize to sites of DNA replication. However, functions for Hdacs1,2 in replication are not known. We used genetic knockdown systems and novel Hdacs1,2-selective inhibitors to systematically determine the contributions of Hdacs1,2 to DNA replication. Knockdown of Hdacs1,2 or inhibition of their activities led to a reduction in the replication fork velocity. Further confirming a role for these enzymes in DNA replication, an increase in replication stress response upon hydroxyurea treatment culminating in DNA damage was observed in cells lacking Hdacs1,2 functions. These observed effects are due to a direct role for Hdacs1,2 in DNA replication as transcription of genes involved in replication or repair are not affected in the absence of Hdacs1,2 activities. We found abrogation of Hdacs1,2 functions affects nascent chromatin structure, as evidenced by the altered sensitivity of newly synthesized DNA to nuclease digestion, and causes an increase in histone acetylation (ac) on chromatin. Specifically, H4K16ac (involved in chromatin compaction) is increased on nascent chromatin in the absence of Hdacs1,2 activities. H4K16ac inhibits the ATPase activity of SMARCA5, an ISWI family chromatin remodeler. We find SMARCA5 associates with nascent DNA and loss of SMARCA5 leads to a decrease in the replication fork velocity similar to the loss or inhibition of Hdacs1,2. Collectively, our studies have revealed important functions for Hdacs1,2 in histone deacetylation, nascent chromatin structure maintenance and regulation of SMARCA5 chromatin remodeler activity, which together are required for the proper progression of the replication fork.

Biography

Bhaskara's research goal is to understand the functions for histone deacetylases (HDACs) in genome maintenance, with the ultimate objective of using the knowledge to improve the therapeutic benefits of HDAC inhibition as a treatment for cancer. In Dr. Bhaskara's post-doctoral research, she made the discovery that HDAC inhibitors induce cancer cell death by directly targeting genome stability independent of their effect of on transcription. She showed HDAC inhibitors trigger genotoxic stress and death only in cycling cells, and thereby, provided a mechanistic explanation for how HDAC inhibitors selectively kill rapidly cycling cancer cells and not the quiescent normal cells. Using genetic deletion systems, she further showed novel functions for Hdac3 in DNA repair, DNA replication and chromatin structure maintenance. Collectively, these findings provided a new paradigm for the mode-of-action of HDAC inhibitors, which are FDA-approved drugs for the treatment of cutaneous T-cell lymphomas. As an independent investigator, Dr. Bhaskara's lab goal is to investigate cellular functions of Hdacs in maintaining genome stability. Dr. Bhaskara did her PhD in Dr. Ranjan Ganguly's lab in University of Tennessee, Knoxville and performed her post-doctoral training at Vanderbilt University, Nashville in Dr. Scott Hiebert's lab.

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