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Valproic acid effects on DNA methylation during the cell cycle of HeLa cells

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Valproic acid (VPA), an anticonvulsant drug that is a histone deacetylase inhibitor, also affects DNA methylation levels. In HeLa cells, the VPA - induced DNA demethylation process involving modified cytosine is a matter of discussion, if by an active pathway, with the participation of ten-eleven-translocation (TET) enzymes, or by a passive DNA replication-dependent pathway. Here, this process was investigated throughout the cell cycle of synchronized and non-synchronized HeLa cells treated with 1 mM and 20 mM VPA for 4 h and compared to the cell cycle of cells treated with 5-aza-CdR, an agent generally used as a passive DNA demethylation control. The methodology used involved flow cytometry, immunofluorescence, ELISA assay and real-time quantitative PCR. The drugs used did not induce cytotoxicity but affected the cell cycle progression. VPA was found to induce over expression of *TET1* and *TET2* genes, decrease in 5mC abundance and increase in 5hmC abundance, either in G1 cells or in proliferative cells. These findings indicate an active pathway performed by VPA in the DNA demethylation process. However, because VPA also affected the *DNMT1* expression, it may also act in the passive DNA demethylation pathway. Although 5-aza-CdR reduced the expression of the *DNMT1* gene, depending on cell proliferation and without affecting the *TET1* and *TET2* gene expression at any stage of the cell cycle, it induced an increase in 5hmC abundance. 5-aza-CdR may thus also act on the active DNA demethylation pathway, because VPA induces reduction in the DNA methylation patterns of non-replicating HeLa cells, a significant potential implication of its use may arise for a therapeutic reversal of DNA methylation in tissues where no further involvement of the cell division process occurs.

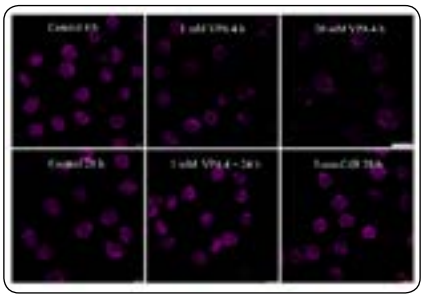

Figure 1: VPA- but not 5-aza-CdR-treatment induced decrease in the nuclear abundance of 5mC in non-proliferative cells

Recent Publications:

1. Veronezi G M B, Felisbino M B, Gatti M S V, Mello M L S and Vidal B C (2017) DNA methylation changes in valproic acid-treated HeLa cells as assessed by image analysis, immunofluorescence and vibrational microspectroscopy. PLoS One 12(1):e0170740.
2. Han B R, You B R and Park W H (2013) Valproic acid inhibits the growth of HeLa cervical cancer cells via caspase-dependent apoptosis. Oncology Reports 30(6):2999-3005.
3. Detich N, Bovenzi V and Szyf M (2003) Valproate induces replication-independent active DNA demethylation. Journal of Biological Chemistry 278(30):27586-27592.
4. Desjobert C, E L Maï M, Gérard-Hirne T, Guianvarc'h D, Carrier A, Pottier C, Arimondo P B and Riond J (2015) Combined analysis of DNA methylation and cell cycle in cancer cells. Epigenetics 10(1):82-91.
5. Sajadian S O, Ehnert E, Vakilian H, Koutsouraki E, Damm G, Seehofer D, Thasler W, Dooley S, Baharvand, Sipos B and Nussler A K (2015) Induction of active demethylation and 5hmC formation by 5-azacytidine is *TET2* dependent and suggests new treatment strategies against hepatocellular carcinoma. Clinical Epigenetics 7(98):1-14.

Biography

Marina Amorim Rocha holds a bachelor's degree in Biological Sciences from the State University of Bahia (UESB) (2015), Campus Vitória da Conquista. She is a Master's degree in Cell and Structural Biology from the State University of Campinas (UNICAMP) (2018). She is currently a PhD student at the State University of Campinas (UNICAMP). Marina Amorim Rocha has expertise in epigenetics, cell cycle, cell proliferation and cytotoxicity and his research purpose while analyzing the cell cycle is to understand some of the epigenetic mechanisms of the VPA action, an anticonvulsant known as a histone deacetylase inhibitor (HDACi) and also proposed an anti-tumorigenic drug, given its ability to inhibit proliferation in some tumor types. Thus, his studies contribute to the understanding of the metabolic pathways performed by VPA and may contribute with advances developed in therapeutic proposals regarding the use of this or similar drugs. Such an idea may especially apply to tissues with no further participation of the cell division process, since it has been shown that in HeLa cells VPA acts independently of DNA replication.

Notes: