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Snakes and rings: Regulation of cellular metabolism

DNA contains the genetic code for all living organisms. The building bricks of DNA are called nucleotides and they have many important functions in all cells. Two very important enzymes for the production of nucleotides are Cytidine triphosphate synthase (CTPS) and Inosine monophosphate dehydrogenase (IMPDH). These two enzymes were found to form cellular mega-structures that can even range from one side of the cell to the other and look like long snakes, rings, hairpins and more. So far, the function of these mega-structures is not fully understood. It is speculated that they can control activity of these enzymes. Because both enzymes are found in higher levels in several cancer cell types, it was investigated which role these structures have in cancer cells and if they can potentially be used as targets in cancer treatment.

CTPS and IMPDH structures form when cells are treated with inhibitors for these enzymes. In this study, we used these inhibitors and a cancer cell line to study characteristics of these structures. We found that these structures form by bundling of several polymers of CTPS and IMPDH. Also, structures made of CTPS can connect with those of IMPDH. The formation and degradation of IMPDH structures happened fast, while CTPS structures remained stable over several hours. Treatment with different nucleosides, precursors of nucleotides, showed diverse effects on CTPS and IMPDH structure formation. All these results show that these structures can form and degrade dynamically. Also, they are controlled by molecules that are used in nucleotide synthesis, which backs up the theory of activity control as function of these structures.

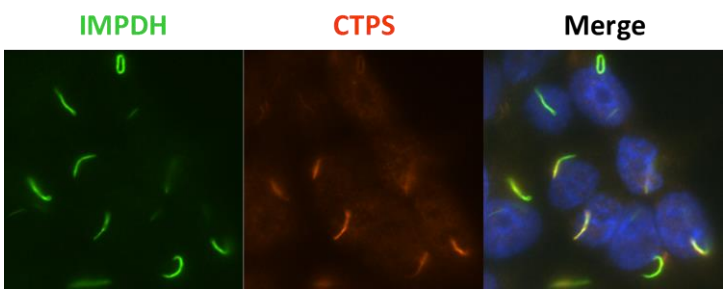

Figure 1: IMPDH (green) and CTPS (orange) can form macro-structures in cells (DNA in cell core stained blue).

In the other part of this study, we focused on the role of CTPS and IMPDH structures in cancer by investigating if a major anti-tumor gene, called p53, is correlated with the formation of these structures. We used two cell lines, HCT116 and SKNSH, both as version with p53 or without it. We found that HCT116 cells without p53 showed increased numbers of structures of CTPS and IMPDH. Also we found that different shapes of IMPDH structures dominated in these cell lines. But we did not cause CTPS or IMPDH filament formation when directly increasing p53 in the cells. SKNSH cells did not show differences in structure formation. In conclusion of these results, we did not find a direct relation between p53 and structure formation. We can assume that the differences in HCT116 cells with or without p53 are caused by differences in levels of these enzymes in cells.

We did not find a direct connection between p53 levels in cells and CTPS or IMPDH structure formation. But our results indicate that these structures indeed are a way of control over these enzymes. Since both enzymes are very vital in cancer cells, further studies might reveal these structures to be targets for cancer treatment.