MTH1 a new anticancer target for neuroblastoma treatment

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Cancer is a highly unpredictable disease, capable of affecting different parts of the human body and usually associate with a harsh medical treatment. Even though there are a lot of blank pages in the book of cancer, there are some traits that start to be well defined. One of this is the high levels of reactive oxygen species (ROS) that drive oncogenic signaling.

Different authors suggest that ROS level can influence, even regulate, processes such as anti-tumor responses in cancer cells, but also cell death or senescence. Many cancers, show increased levels of the MutT Homolog1 (MTH1) enzyme to counteract the high levels of oxidative stress that present. This enzyme sanitizes dNTP pools eliminating 8-oxo-7,8-dihydro-2´-deoxyguanosine triphosphate (8-oxoGTP), in order to prevent its incorporation during DNA replication. MTH1 in non-essential in normal cells, but a recent study demonstrates that MTH1 function is essential in cancer cells to avoid the incorporation of oxidized dNTPs; that would lead to DNA damage and cell death. This is the reason because MTH1 has been proposed as a selective anticancer target.

In our group, we are using different MTH1 inhibitors to treat one specific type of cancer: neuroblastoma. Neuroblastoma is a pediatric cancer arising from sympathetic nervous system. One of the best known features of this cancer is the heterogeneity in outcome. Amplification of the oncogene MYCN is related with unfavorable prognosis.

In the first part of our study, we treat three neuroblastoma´s cells lines with MTH1 inhibitors: TH588 and TH1579. After the treatment, we observed reduction in viability levels as well as increased DNA damage in all of them. In view of this result we can hypothesized that MTH1 has an essential role in neuroblastoma cancer cells, though, right now, we cannot conclude anything about the mechanism behind.

Due to the high rate of mortality of neuroblastoma, we are also working on developing new therapies to treat these tumors. Since we know the potential of MTH1 inhibitors, we are trying to combine them with a panel of chemotherapy drugs and DNA repair inhibitors. Of interest a promising combination showing synergistic effect in MYCN amplified neuroblastoma cells was to combine MTH1 inhibitor with a DNA-PK inhibitor (NU7026).

Although our results are quite preliminar, our data could open novel ways for the treatment of high risk neuroblastoma tumors.

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