SPETSES SUMMER SCHOOL

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SPETSES ISLAND, GREECE

CANCER EPIGENETICS: PRINCIPLES, APPLICATIONS AND SINGLE-CELL RESOLUTION

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SFB1064 Chromatin Dynamics

REPROGRAMMING CANCER · OMPROGRAMMERING AV KREFT

UiO : CanCell University of Oslo

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Influence of PARP inhibition on 5-hmC level in NSCLC

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5-hydroxymethylcytosine (5-hmC) is formed through the oxidation of 5-methylcytosine (5-mC) by the catalytic activity of TET enzymes. It has been proposed to have regulatory functions as an independent epigenetic mark and it might have diagnostic potential as global loss of 5hmC level is commonly observed in cancers.
We have recently shown the inhibitory influence of PARP-1 dependent PARylation on TET1 hydroxylase activity in DNA demethylation. These findings could provide the rationale for using PARP inhibitors in cancers that are characterised by the 5hmC loss, other than cancer where treatment with PARP inhibitors exploited homologues repair (HR) defects on the basis of the synthetic lethality phenomenon. The activating effects of PARP inhibition on TET activity could provide the additional mechanism of action of PARP inhibitors (which are less cytotoxic than standard chemotherapeutic agents) in the treatment of cancers characterised by diminishing levels of 5hmC.
In our study, we have tested the effects of PARP inhibition on 5-hmC levels in non-small cell lung cancer. First, we analysed global levels of 5-hmC in several non-small cell lung cancer cell lines (NCI-H460 sensitive and resistant to doxorubicin, A549, NCI-H661) in comparison to normal fetal lung fibroblast cells MRC-5. Since both slot-blot and confocal microscopy analyses have shown that the A549 cell line has the lowest level of 5-hmC this cell line was selected for further experiments in which we set out to raise DNA hydroxymethylation levels by inhibiting PARP activity. After 72h treatment of A549 cells with PARylation inhibitor niraparib (IC50= 10 μM), we indeed observed an increase in 5-hmC level while 5-mC level did not change. This is a promising start to our investigation of alternative mechanisms of action of PARP inhibition in the treatment of cancers. Through this research, we hope to expand the range of cancer types that would be treated with PARP inhibitors, regardless of the HR status.

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