LUXEMBOURG INSTITUTE OF HEALTH
RESEARCH DEDICATED TO LIFE

UNIVERSITÉ DU LUXEMBOURG

LECTURE SERIES & WORKSHOPS 2019

CANCER RESEARCH

20
JUNE 2019
Thursday

LECTURE
CHL Luxembourg
Amphitheatre
11.00 - 12.00 pm

MEET, GREET & EAT *
light lunch provided
CHL Luxembourg
Foyer
12.00 - 1.00 pm

9 10 11 12 1 2 3 4

* Registration is mandatory by sending an email to florence.henry@lih.lu

SPEAKER

Prof Christine SERS

Professor for Tumor Systemsbiology,
Charité, Universitätsmedizin Berlin;
Institute of Pathology, Germany
Group leader of the international research group Molecular Tumor Pathology & Tumor Systems Biology
Charité, Universitätsmedizin Berlin;
Institute of Pathology, Germany

HOST:
LIH

RESPONSIBLE LIH SCIENTIST:
Gunnar Dittmar
(gunnar.dittmar@lih.lu)

TARGETING RAS IN COLORECTAL CANCER

ABSTRACT

RAS mutations occur early in colorectal cancer (CRC) development and mutations are homogenously distributed throughout tumor samples, rendering RAS an ideal therapeutic target.
RAS was discovered more than two decades ago, yet no targeted drug has made it into the clinic until now. Consequently, targeting RAS downstream effector proteins and mechanisms has turned into an attractive option for advanced treatment of patients. Histone deacetylase inhibitors (HDACi) are considered as a promising novel therapeutic approach in the light of their potent tumour-selective effects. Their use for treatment of CRC, however have until now demonstrated limited success as a monotherapy in clinical trials. To shed further light on this, the involvement of oncogenic RAS as a key driver of CRC, in determining the responsiveness to HDACi has been explored. Using cell culture models harboring conditional oncogenic NRAS or KRAS we uncovered an oncogenic RAS-dependent resistance mechanism characterized by the induction of a reversible senescence-like growth arrest. This proved to function as a fail-safe method allowing RAS-mutant cells for re-entry into cell cycle following the withdrawal of HDACi. The mechanism by which this is proposed to occur is via the phosphorylation of c-MYC, priming it for ubiquitin-mediated proteosomal degradation. While mutant RAS proteins are expressed in every cell of a tumor sample, a strikingly heterogenous response to HDACi was found in CRC canceroids. These findings may confer important clinical implications, and in addition further aid the development of a rational combinatorial therapeutic strategy using HDACi in solid cancers.

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