LECTURE SERIES 2023
CANCER RESEARCH

LUXEMBOURG INSTITUTE OF HEALTH | UNIVERSITÉ DU LUXEMBOURG

16 MAR 2023
Thursday

LECTURE *
11.00am - 12.00noon

MEET & EAT *
Light lunch provided
12.00 - 1pm

6 7 8 9 10 11 12 1 2 3

Metabolic and mitochondrial adaptations driving drug resistance in cancer: from basic studies to clinical perspectives

ABSTRACT

Despite recent therapeutic breakthroughs, therapeutic resistance remains the major barrier in the treatment of patients with acute myeloid leukemia (AML) and is responsible for frequent relapse in these patients. Therefore, understanding and targeting the causes of drug resistance represent an urgent need in the development of new treatments selectively eradicating drug-resistant/tolerant AML cells responsible for relapse (hereafter Relapse-Initiating Cells or RICs) and overcoming patient relapses. In this context, we have shown that hyperactivation of mitochondrial oxidative metabolism plays a crucial role in drug resistance of AML and targeting elevated oxidative phosphorylation (OxPHOS) activity with direct and indirect mitochondrial OxPHOS inhibitors sensitizes resistant cells to cytarabine (AraC) in AML. In fact, high OxPHOS phenotype is the consequence of an enhancement of mitochondrial activities due to an increase in respiratory substrate and cofactor (NADH, calcium, iron) availability, mitochondrial machinery (biogenesis, mitochondria transfer from stromal cells), mitochondrial BCL2 dependency and ROS detoxification upon inflammatory and stress responses. In addition, the activation of a cAMP-mediated signaling pathway and ATF4-driven mitochondrial stress response leads to the induction of expression of key master regulators of mitochondrial biogenesis and homeostasis in RICs. Genetic or pharmacological inhibition of ATF4 or PKA expression/activity blocks mitochondrial reprogramming triggered by AraC treatment and markedly enhances its cytotoxicity in AML cells *in vitro* and *in vivo*. Interestingly, this ATF4-OxPHOS axis is also implicated in the resistance to new therapeutic combinations such as IDH inhibitor or BCL2-selective inhibitor venetoclax (VEN). Especially, targeting AraC-induced overexpression of BCL2 with VEN led to a decrease in mitochondrial matrix calcium, TCA cycle activity and OxPHOS observed upon AraC treatment. This regimen primed AML cells to caspases-dependent apoptosis and enhanced anti-AML effects of AraC *in vivo* and in patients from clinical trials. Importantly, single cell RNAseq further uncovered three distinct cell subpopulations with electron transport chain complex (ETC) and TP53 pathway as amenable vulnerability. Accordingly, treatment of VEN+AraC-resistant AML cells with mitochondrial inhibitors such as ETCI inhibitor IACS-010759, pyruvate dehydrogenase inhibitor CPI-613 (devimistat) or the mitochondrial ClpP protease agonist ONC-212 significantly extended the time-to-relapse after VEN+AraC *in vivo*. In summary, adaptive response to mitochondrial stress induces mitochondrial recovery and promotes pleiotropic drug resistance in AML. Together, our work provides scientific rationale to develop drugs targeting the mitochondrial metabolism to further enhance the vulnerability of AML cells to currently approved therapies, especially in clinics in patients relapsing or non-responsive to chemotherapy or after failure of frontline VEN regimen (40% of AML patients). Now, our aims are to address whether specific diets might control cell capacity to mitochondrial adaptation that supports resistance to therapy and relapses in patients. This knowledge will help and guide physician expectations and patient management with more personalized approach through the identification of the patient mitochondrial profile best suited for the highest clinical efficacy of drug combination in AML patients.

SPEAKER

Dr Jean-Emmanuel Sarry
Cancer research center of Toulouse, France

HOST:

Department of Cancer Research (LIH)

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***Please note that registration is mandatory by sending an email to siu-thinh.ho@lih.lu**

Locations:

Lecture
CHL - Centre
Room: ***Amphitheatre***
4, rue Ernest Barblé
L-1210 Luxembourg

Meet & eat
LIH - DoCR (BAM)
Room: ***Robin Holliday***
6A, rue Nicolas-Ernest Barblé,
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