Séminaire

Institut de Biologie Structurale

CONFÉRENCIER INVITÉ

Mardi 03 Juillet 2018 à 11h

Chadwick Amphitheater ILL

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Therapeutic targeting of acetylation-dependent circuitries in cancer

Transcriptional programs are often deregulated in disease, offering opportunities for therapeutic intervention. One of the most promising over recent years is through targeting epigenetic readers of the bromo and extra-terminal (BET) family. Despite the successful translation of BET-inhibitors into the clinic, emergence of toxicity and resistance necessitate better understanding of the underpinning biochemistry, in order to develop safer therapeutics. I will discuss our efforts to understand the molecular basis of BET-initiated interactions leading to the recruitment of transcriptional effectors onto chromatin, seeking to therapeutically exploit this axis. We have established a high throughput biophysical platform that has allowed for the development of selective and nonselective tool chemical compounds that modulate the acetylation dependent readout of BET proteins, helping interrogate their function in complicated solid and hematopoietic tumour systems. We find BETs linked to large complexes associated both with transcriptional activation as well as suppression of key survival programmes, and identify shared and distinct structural determinants leading to complex assembly both in acetylation-dependent and independent manner. Our work has highlighted several unexpected connections initiated via acetylation-independent interactions as well as rewiring following chemical inhibition, identifying novel protein functions and gene expression modulated via inter-regulation of BET proteins and competition for common targets. Our data point towards an under-appreciated role of modularity within BETs in linking transcriptional attenuators to chromatin, revealing protein-specific contributions into complex assembly and informing into potential combination therapies stemming from better understanding of pharmacological rewiring of acetylation-dependent readout, thus providing novel points for intervention in a clinical setting. Our work on BETs can provide a paradigm to understand epigenetic processes so that we can target the specific rather than the general, contributing to the long term goal of tailoring therapy and stratifying patients, aiming to address a major challenge in tumour biology, increasing selectivity while avoiding resistance.

Hôte : Winfried Weissenhorn

L'accès au campus EPN nécessite un avis de rendez-vous

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