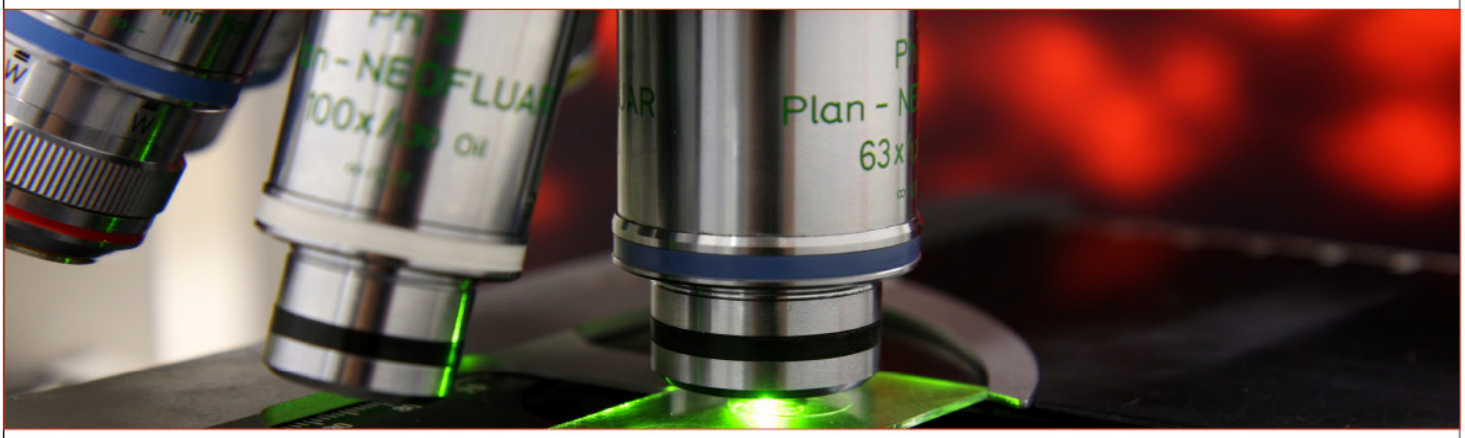
SÉMINAIRES ET CONFÉRENCES



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Structural characterization of the mechanism driving oncogenic BRAF activation

Uncontrolled activation of the RAS-RAF-MEK-ERK signaling pathway is a key driver in tumor development and sustained growth. In many cases, this is triggered by oncogenic mutations in the BRAF gene. Due to BRAF's pivotal role in human cancers, extensive research has focused on understanding its regulation and developing targeted therapies to mitigate its pathological effects. Recent structural studies have provided insights into the normal activation mechanism of BRAF. However, the precise mechanism by which oncogenic mutations activate BRAF kinase activity remains unclear. To address this gap, we used cryo-electron microscopy (cryo-EM) to resolve the 3D structures of several oncogenic BRAF mutants, including the most prevalent variant, BRAF V600E. Surprisingly, our findings revealed that all oncogenic mutations disrupt an inhibitory interaction between BRAF's cysteine-rich domain (CRD) and its kinase domain—an interaction characteristic of the autoinhibited, monomeric BRAF in unstimulated cells. This disruption leads to a reorientation of the kinase domain into a conformation resembling a pre-activated state. Mechanistically, the key event appears to be the displacement of helix αC within the kinase domain by oncogenic mutations, triggering a substantial conformational shift that results in a pre-activated monomeric state. Furthermore, we found that PLX8394, a BRAF inhibitor that stabilizes helix αC in its out-inactive conformation, can reverse the effects of oncogenic mutations by re-establishing the autoinhibitory interaction between the CRD and kinase domain. In addition to shed light on the mechanism underlying oncogenic BRAF activation, this study suggests a novel design principle for developing a new generation of compounds as stabilizers of the BRAF autoinhibited state.

Lundi, 28 avril 2025, 11h30

Pavillon Joseph-Armand-Bombardier, Salle : 1035

ET

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