SÉMINAIRES ET CONFÉRENCES

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« Structural basis of Ras inactivation by Neurofibromin»

Ras is a small GTPase whose role as a central switch in cellular signaling has placed it at the core of several human diseases. As other GTPases of its kind, Ras activity is dependent on its nucleotide state: the GTP-bound form is active, driving cellular proliferation, while hydrolysis of the GTP into GDP leads to Ras inactivation. One key regulator of Ras signaling, Neurofibromin (NF1), was discovered for its role in Neurofibromatosis type I, a genetic disease involving dermatological and neurological symptoms, as well as predisposition to cancer. NF1 is a 320kDa protein, containing a GAP-related domain (or GRD), and is one of the best characterized GTPase activating proteins (GAP) for Ras. As such, it is a negative regulator of Ras and a tumor suppressor gene. Due to its large size, structural characterization of the entire protein has remained challenging until now. Here, we present the cryo-EM structure of full-length NF1 which forms a figure-eight-shaped homodimer. We have determined the structure of NF1 in two main functional states: an auto-inhibited state, where the GRD domain is in a conformation that is mutually exclusive with Ras binding, and an activated state compatible with RasGAP activity. This conformational change is controlled by the presence of allosteric guanosine nucleotide binding site located between the GRD and Sec14 domain, the same site which locks the GRD domain into its closed state, suggesting NF1 senses the amount of guanosine nucleotides in the cell. These structures now allow for the in-depth analysis of the several hundred mutations that are known to cause neurofibromatosis type I. We establish the molecular basis for the effects of many disease-causing mutations, which destabilize the protein thereby causing Ras hyperactivation in the cell.

Le lundi 22 mars 2021, 11h30

Invité de Pascale Legault

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