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LES SÉMINAIRES DE L'INMG

The tumor suppressor LKB1 controls cell fate through pyruvate-alanine transamination

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Vendredi 1er Décembre 2017

11 heures

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Abstract :

The tumor suppressor *LKB1* (also named *STK11*) codes for a serine/threonine kinase. LKB1 acts as a key regulator of cell polarity as well as energy metabolism partly through the activation of the AMP-activated protein kinase (AMPK), a sensor that adapts energy supply to the nutrient demands of cells facing situations of metabolic stress.

To determine if Lkb1 exerts a coordinated regulation of energy metabolism and cell polarity, we deleted the *Lkb1* gene in polarized cells and explored the metabolic consequences. In particular, we generated spatio-temporal ablation of *Lkb1* in a subpopulation of mouse embryonic multipotent neural crest cells (NCC) that originate from the neural tube and give rise to a broad range of derivatives including most of the face, the melanocytes, the peripheral nerves and the enteric nervous system (ENS). Mutant mice exhibited craniofacial malformations, hypopigmentation, intestinal pseudo-obstruction and hindlimb paralysis. Further phenotypic characterization revealed that LKB1 is required for the differentiation and maintenance of two NCC-derivatives, Schwann cells and the ENS. Using a model of neural crest stem cell line, we demonstrated that Lkb1 is key for neural crest-derived glial commitment. Mechanistically, *Lkb1* loss led to an increase of alanine and glutamate levels and inhibition of pyruvate-alanine transamination rescued glial differentiation of *Lkb1*-null NCC, in a mTOR dependent manner. Furthermore, AICAR, an analogue of AMP, rescued glial differentiation of *Lkb1*-deficient NCC and corrected the Schwann cells and ENS phenotypes of *Lkb1* mutant mice.

Altogether, these findings highlight the central role of Lkb1 during neural crest cell lineage and uncovered a link between Lkb1-mediated pyruvate-alanine cycling and glial commitment. These results provide also new insights for the understanding of metabolic events that contribute to the formation of *LKB1*-deficient malignancies.