Institut Européen de Chimie et Biologie

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Regulation of Rnd3 expression in tumor cells

Léo Piquet
BaRITon, INSERM UMR1053 (Equipe V. Moreau), Bordeaux, FRANCE.

Rnd3 protein is an atypical member of the Rho GTPase family, devoid of GTPase activity and constitutively active and bound to GTP. Rnd3 regulation does not occur through the classical GTPase cycle but is achieved at transcriptional, posttranscriptional or translational level. Rnd3 is underexpressed in hepatocellular carcinoma (HCC), and this down-regulation increases HCC cell invasion and is linked to HCC progression. The aim of this thesis project was to better decipher the mechanisms involved in Rnd3 expression in tumor cells, and particularly in HCC cells. In a first part, Rnd3 regulation by β-catenin was studied. β-catenin is found mutated in one third of HCC, and activating β-catenin mutations in human HCC correlates with the lowest levels of Rnd3. An original model established in HepG2 cells allowed the study of the involvement of WT β-catenin versus mutated β-catenin in the regulation of Rnd3 expression. Interestingly, our results demonstrated that both forms of ß-catenin independently regulate Rnd3 mRNA expression. The WT β-catenin regulates Rnd3 at the transcriptional level, whereas the mutated β-catenin acts through the 3'UTR of Rnd3 mRNA. The second and main part of this thesis project was the study of the regulation of Rnd3 expression by the mechanotransduction pathway MRTF/SRF. The activation of this signaling pathway is tightly regulated by actin cytoskeleton, and the MRTF/SRF pathway directs in return the expression of a huge number of genes involved in actin dynamics. Our results uncovered Rnd3 as a new direct target of MRTF/SRF pathway in tumor cells. Indeed, upon actin dynamics changes, MRTF/SRF is able to bind Rnd3 promoter in order to favor its expression. As Rnd3 also acts as a regulator of the actin cytoskeleton, our results highlight Rnd3 at the center of a feedback loop of the MRTF/SRF mechanotransduction pathway. Taken together, all of the results obtained helped to better decipher the mechanisms of Rnd3 regulation in tumor cells.