Molecular mechanisms of the inhibition of the Rho/ROCK/LIMK2/cofilin pathway by the SecPH domain of Neurofibromin, Nf1, the protein responsible for Neurofibromatosis type I

P-02.5-33

B. Vallée[I], M. Thomas[II], L. Blot[I], K. Lesage[I], F. Godin[I], M. Doudeau[I], H. Bénédetti[I]

[I]CBM-UPR4301 CNRS, ORLEANS, France, [II]University of Goteborg, Goteborg, Sweden

Cell signalling transduction pathway crosstalks allow fine regulation of the fate of the cell. In a previous study, we have shown an interconnection between Ras and Rho signalling pathways via the interaction between the RasGAP Nf1 and the kinase LIMK2 downstream of Rho. We then demonstrated that the SecPH domain of Nf1 prevents LIMK2 activation by ROCK, its upstream regulating kinase (Vallee et al. (2012) PLoS One 17;7(10):e47283). We went further into the characterization of this interconnection by determining the molecular mechanisms involved into this process. We identified the domains of each protagonist involved into this interconnection and showed that the SecPH domain of Nf1 as well as the KINASE domain of ROCK interact with the same two domains of LIMK2, its SP/PDZ and KINASE domains. We demonstrated that the SecPH domain of Nf1 abolishes the interaction between the KINASE domains of ROCK and LIMK2, preventing the phosphorylation and subsequently the activation of this latter by the precedent. Our findings bring new insights into the understanding of the regulation of the Rho/ROCK/LIMK2/cofilin pathway by the RasGAP Nf1, and could open new therapeutic perspectives for Neurofibromatosis type I treatment, as this regulation is impaired in this disease.