A New Mechanism Of Regulation Of LIMK1 And LIMK2, Kinases Involved In Cytoskeleton remodelling

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LIMK1 and LIMK2, LIMKs, are the only two members of the LIMK family. They are dual kinases as they phosphorylate both Serine/Threonine and Tyrosine. They are involved in cytoskeleton remodelling by promoting actin filament formation via the phosphorylation and subsequent inhibition of cofilin, an actin depolymerizing factor. They are also involved in microtubule turnover, but the molecular requirements of this action still remains to be elucidated. LIMK1 and LIMK2 play a crucial role in many physiological processes, such as migration, motility, division, apoptosis, and neurite plasticity. Their role in many diseases has been established: cancer, neurological disorders, Neurofibromatosis, pain, erectile defects, and inflammation. LIMK1 and LIMK2 belong to the Rho, Rac, CDC42/ PAK, MRCK, ROCK signalling pathway. They are phosphorylated and activated by upstream kinases on their Thr508 for LIMK1 and Thr505 for LIMK2. Here, we show that this canonical well-described activation is necessary but not sufficient for LIMK optimal activity on cofilin. Indeed, we unravel a new unsuspected mechanism of activation of these kinases via their C-terminal extremity. We point out a major role of a Tyr, required for LIMK dimerization and trans-phosphorylation, prerequisite of LIMK phosphorylation on their Thr and triggering their stability. These new mechanism of regulation of LIMKs may pave the way to new therapeutic strategies targeting these kinases as so far they remain undruggable proteins.