The non-receptor tyrosine kinase Fes promotes the growth and the metastatic progression of neuroblastoma tumor

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Neuroblastoma (NBL), the second most common extracranial solid tumor in childhood, is characterized by the cancerous transformation of immature, neural crest-derived, sympathetic neuroblasts, which have lost their ability to differentiate into mature cells. NBL is remarkable for its biologic heterogeneity and broad range of clinical behavior. Despite advances in multimodal therapy, prognosis for patients with high-risk NBL remain poor.

In the attempt to identify new targets for the therapy of this tumor, we have recently focused our attention on the expression and function of the non-receptor tyrosine kinase Fes in human NBL cell lines, since this protein is known to exert transforming or tumor suppressive functions depending on the district of expression.

In our models, we found that Fes is expressed in a limited population of cells within both human NBL cell lines and tumor biopsies, which display a more aggressive phenotype. Indeed, Fes positive cells showed increased viability, proliferation and capacity to form spheres in anchorage-independent conditions. Furthermore, we demonstrated that IGF-I may recruit STAT3 down-stream of its signaling pathway only in presence of functional Fes thereby influencing the metastatic potential of such tumors. Indeed, IGF-I, already known to be relevant for NBL progression, causes a Fes-dependent activation of STAT3, thereby leading to the expression of factors having an impact on NBL microenvironment, i.e. IL10, VEGF. In line with these observations, we also demonstrated that Fes supports NBL migration, since the activation of this kinase enhances IGF-I induced motility of NBL cells in 'wound-healing' assays.

In summary, our work provides the first evidence of the involvement of Fes in the progression of NBL. These results broaden the knowledge of NBL biology and of the interactions of this tumor with the host. Nevertheless, the identification of a specific molecular pathway could pave the way to novel therapies, more effective and less toxic than conventional ones.