Medulloblastoma, tumor of the cerebellum: novel in vivo models and preclinical therapies

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We are studying since many years the process of development of the cerebellum and of its tumor, medulloblastoma (MB), which arises from a developmental misregulation and pathology of the cerebellar granule cell precursors (GCPs). GCPs proliferate in the cerebellar external granular layer (EGL) and then migrate inwardly, forming the internal cerebellar layers. We study a MB subtype carrying activation of the Sonic Hedgehog pathway (Shh-type), which makes GCPs prone to transformation and to tumorigenesis. In fact, Patched1 heterozygous mice (with activated Shh pathway) are spontaneously developing low frequency MB. This tumor hits mostly children and is very difficult to cure, as standard treatment with radiotherapy and chemotherapy after surgical resection frequently leaves permanent cognitive damage in young patients. Thus, new, less aggressive therapies are needed.

We have previously identified the antiproliferative gene Tis21 as a MB-suppressor gene, by demonstrating that a Patched1+/− mouse model with conditionally activated expression of Tis21 in GCPs, generated by us, shows a significant reduction of MB frequency (1). The underlying mechanism relies on the ability of Tis21 to selectively inhibit cyclin D1 expression. Given that a down-regulation of Tis21 is observed in human MBs, we also generated a new Patched1 heterozygous mouse model with deletion of Tis21 (Patched1+/−-Tis21KO), and observed that it develops MB with high frequency (about 85%) (2). By genomic analysis we identified as responsible for the increased MB penetrance a defect of migration of the GCPs out of the proliferating region of the EGL, consequent to reduced expression of the chemokine Cxcl3. We observed that Cxcl3 is transcriptionally activated by Tis21 and it drives the GCPs to migrate out of the EGL, thus making the GCPs less prone to the transforming local influence of Shh (2).

In view of these findings, we recently performed two preclinical experiments involving Tis21 and Cxcl3. Concerning Tis21, by means of an adeno-associated virus (AAV) vector, we vehiculated Tis21 to MB tumor cells allotransplanted into the flank of immunodepressed mice, and observed a strong decrease of MB growth and proliferation (3). As for Cxcl3, we found that the chronic intracerebellar administration of Cxcl3, for 1 month, in the high frequency MB model Patched1+/−-Tis21KO, prevents totally the growth of medulloblastoma lesions by forcing neoplastic cells to migrate and differentiate (4).

We are currently analyzing the effect of chronic intracerebellar administration of Cxcl3 in older high frequency MB mice (3-month-old), in order to check the ability of Cxcl3 to counteract MB development at more advanced stages.

Since Cxcl3 is not toxic and is well tolerated, we hope that these studies may lead to a novel therapy, which could be used alone or together with other anti-MB drugs.

References:

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