Plant virus nanoparticles as an innovative platform for targeted drug delivery to medulloblastoma

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Plant viruses have proven to be excellent candidates for different applications in nanomedicine, such as drug delivery. In this context, we are characterizing the Tomato Bushy Stunt virus (TBSV) as drug-vehicle to the Sonic Hedgehog-dependent medulloblastoma (SHH-MB), the brain tumor variant, arising in young children (<3 years of age), with the highest risk of unfavorable outcome. TBSV, member of the genus *Tombusvirus*, is an icosahedral virus of 32 nm in diameter made up of 180 subunits of the coat protein (CP), and can be modified on the surface to expose polypeptides genetically fused to the *cp* gene, as well as in the inner to load specific cargos. TBSV NPs, displaying tumor targeting peptides, were produced in *Nicotiana benthamiana* plants, purified, loaded with the drug Doxorubicin and tested on primary cultures of Shh-MB cells and on their cerebellar precursors, both derived from *Patched1*$^{+/-}$ knockout mice, the most widely studied model of MB. These *in vitro* experiments allowed to define the peptides most efficient in promoting the specific uptake of viral NPs, and to demonstrate that the delivery of Doxorubicin through TBSV reduces of 5 folds the dose of the chemotherapeutic necessary to obtain a 90% decrease in tumor cells viability. Moreover, the systemic administration of TBSV NPs in MB symptomatic *Ptch1*$^{+/-}$ mice confirmed the ability of the virus particles to specifically reach the tumor and gave also encouraging results on their therapeutic effect on pre-neoplastic lesions.