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Are B7-H3 CAR-T cells the future universal treatment for pediatric brain tumors?

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See the article by Haydar et al. in this issue, pp. 967–978.

Many malignant pediatric brain tumors fall in the category of resistant malignancies that deserve to be treated by innovative approaches. Immunotherapy with T-cell-expressing chimeric antigen receptors (CAR-T) is a promising perspective to overcome this resistance to classical treatments. Among immune response-based therapies, CAR-T approach is all the more justified that tumors lack class I MHC (major histocompatibility complex) expression—which is indispensable for HLA (human leukocyte antigen)-based immune response but not for CAR-T therapy. In this issue, Haydar et al. first report that pediatric non-glioma brain tumors under-express HLA class I,[1] which may underline the poor response to immune checkpoint inhibitors seen in pediatric malignancies, and would support the development of CAR-T rather than any other type of immunotherapy. However, while CD19 CAR-T therapies have shown some efficacy in pediatric and adult B-cell malignancies, no approval has been obtained for treatment with CAR-T of any solid tumor so far, due to the lack of response in clinical trials. Indeed, the development of CAR-T cell therapy in solid tumors faces additional challenges. The first challenge is the identification of the specific antigens to target; the best antigen candidates would i) be highly and homogeneously expressed in tumor cells ii) show a limited inter-tumor heterogeneity, and iii) display weak to null expression in normal tissue. In adult brain tumors, several studies have identified ILR-13Ra2, HER2, ephrin type A-receptor 2 (EphA2), B7 homolog 3 (B7-H3), and disaloganglioside (GD2) as cell surface antigens recurrently expressed, and, thereby, potential good candidates for CAR-T therapies. Here, Haydar et al. hierarchize these 5 potential CAR-T targets within pediatric brain tumors. Taking advantage of a unique collection of patient-derived orthotopic xenografts (PDOX), the authors rank cell surface antigens according to the homogeny and the level of protein expression assessed by flow cytometry and immunohistochemistry. Thereby, B7-H3 pops up as the most promising target. Its lack of expression in normal brain, its high level across tumor types, and its homogeneous expression within each individual tumor make it a theoretically perfect candidate for CAR-T therapy. The results reported here are roughly in agreement with previous publications, depicting a very similar landscape for B7-H3 expression throughout pediatric brain tumors.[2–4] Haydar et al. found the highest expression of B7-H3 in high-grade glioma and medulloblastoma PDOX; surprisingly, however, they observed no expression in atypical teratoid rhabdoid tumors, in disagreement with previous publications.[3,4] However, given the broad expression across tumor types, these results emphasize the relevance of pursuing on with these targets toward clinical studies.

Once a relevant target is identified, the next issue is to ensure that CAR-T cells will reach the tumor site, which remains challenging in solid tumors, in general, and brain tumors, in particular. Local delivery, in the tumor or in the ventricle, is studied as a potential way to circumvent this putative obstacle. Here, the authors do not compare the efficacy of local vs intravenous administration of CAR-T; however, they observe that intravenous administration of B7-H3 CAR-T in mice is efficient in controlling the tumor growth in a Sonic Hedgehog subtype of medulloblastoma PDOX. This brings quite original data in the field, where most authors advocate in favor of locally delivered CAR-T cells to increase the chance of efficacy. Whether the effect will sustain long enough to definitely cure mice—and children, once these CAR-T cells will eventually be used in the clinics—remains to be demonstrated. The last but not least issue is the toxicity of the CAR-T strategy. Here, the authors note no remarkable toxicity in mice treated with mouse B7-H3 CAR-T cells, in particular, no brain injury in 4-week-old mice. In line with previous reports,[5] these results finally support the clinical development of B7-H3 CAR-T cells. A specific attention will still need to be paid to the youngest patients. Being widely expressed in pediatric brain tumors and not in young (mouse) brains, B7-H3 may thus provide one of the most promising targets for CAR-T cell therapies in pediatric brain tumors; still, the issue of delivery, sustainability, and lack of toxicity remains to be fully evaluated by the forthcoming clinical trials.

Conflict of interest statement. The author declares no competing interests.

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