



In Focus

Neural Stem Cell Carriers for the Treatment of Glioblastoma Multiforme



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Grade IV astrocytoma, termed glioblastoma multiforme (GBM) is one of the most aggressive malignancies known to man. Despite intensive therapies, the median survival has remained approximately 15 months. One of the major challenges to the treatment of CNS malignancies is the blood brain barrier (BBB). The barrier is designed to be incredibly selective, which means few therapeutics given to patients will reliably arrive at the site of the malignancy. To overcome the BBB and low blood flow that tends to occur within these tumors, various biodegradable materials, polymers and nanoparticles that can slowly release therapeutics at the site of the tumor have been developed. In the past, various chemotherapies have been attempted to be delivered in this way (Kane et al., 2015). The major problem with direct treatment of tumors is the low amount of diffusion and inefficient delivery of therapeutics. There have been attempts at enhanced delivery using convection based therapies, which until this point have not generated significant survival advantage in patients. Furthermore, the diffuse nature of the tumor means it may spread far from the treatment site. It is for these reasons that a carrier with a high amount of versatility and tumor-homing capability is urgently needed.

Beginning with a critical discovery in 2000, it was demonstrated that neural stem cells (NSCs) have intrinsic glioma-tropic properties, even to distant sites (Aboody et al., 2000). Since this initial finding, NSCs have been manipulated in a number of ways to elicit anti-cancer effects. First, NSCs can be engineered to produce different genes. In a pioneering preclinical study, Dr. Aboody's laboratory generated an NSC cell line carrying cytosine deaminase (CD). After systemic treatment with the pro-drug Gancyclovir (GCV), the suicide gene converts the GCV into its toxic di (and tri) phosphate form only where the NSCs have migrated. This has provided significant efficacy in a pre-clinical model of GBM while preventing off-target toxicity (Aboody et al., 2013). A phase I clinical trial utilizing this approach has recently completed accrual (Clinical Trial Identifier – NCT02015819). Other groups have generated NSC cell lines with other anti-cancer agents. NSCs expressing the anti-tumor molecule TRAIL (tumor necrosis factor-related apoptosis-inducing ligand) have recently come back into focus after groups have been able to sensitize glioblastoma cells to TRAIL using a number of novel compounds such as the cardiac glycoside lanatoside C and the histone deacetylase inhibitor MS-275 (Teng et al., 2014; Bagci-onder et al., 2013). Both therapies are thought to function by influencing alternative

death receptor (DR) expression on the surface of glioblastoma cells, thus providing alternative targets for TRAIL induced cell death.

Other than directly modifying the NSC, these cells can also be loaded with therapeutic cargo. Our group had previously loaded NSC with mesoporous nanoparticles containing doxorubicin, attached via a pH sensitive linker (Cheng et al., 2013). This targeted release of chemotherapeutics had significant impact on animal survival in a mouse model of glioma. Other nanoparticles have also been successfully loaded into NSC, for example another group loaded gold nanorods (AuNR) onto NSC carriers, which enhanced the distribution of the nanoparticles to the tumor tissue (Mooney et al., 2014). After treatment with near-infrared radiation, the gold nanoparticles convert light to tumor-killing heat, which therapeutic effect covers a significantly larger area than injection of particles alone.

The use of NSC carriers has recently been extended into the loading of adenoviruses. By allowing either the infection or replication only within cancer cells, the use of recently developed conditionally targeted or replicative adenoviruses (CRADs) has become an attractive modality for treatment. This allows for a “1–2 punch” of both oncolysis and enhanced delivery of therapeutics, while also minimizing off-target toxicity. By loading a conditionally replicative adenovirus (CRAD-Survivin-pk7) onto NSC carriers, we have demonstrated enhanced anti-tumor efficacy compared to viral treatment alone (Ahmed et al., 2013). Previous studies have been performed to suggest this modality of CRAD delivery is efficacious and is currently planned for a phase-I clinical trial.

The route of delivery of NSCs is critical for an efficacious therapy, because the amount of NSCs that can make it to the glioma tissue is highly dependent on their route of administration. In murine models of GBM, injection of NSCs contralateral to the tumor site causes their migration and efficient delivery of therapy (Ahmed et al., 2013). The problem in human patients is that intratumoral injections are invasive and troublesome for repeat injections. While intravenous administration of NSCs can still cause migration to the tumor site, the efficacy of this route remains controversial. Recently, as a way to curtail these limitations, it has been demonstrated that NSC can be delivered intra-nasally and efficiently migrate to the tumor tissues. The intranasal route allows for repeat administration and has higher amounts of NSC migration (Schmidt et al., 2014).

These methods of direct treatment to the tumor have advanced significantly from simply administering drugs directly to the tumor site. Stem cells and the therapies they carry provide a powerful new platform for treating malignancies. The field of cellular carriers is still

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in its infancy, and there are still many obstacles to overcome for this therapy to become successful. It is important to note that the loading of adenoviruses into NSCs enhances survival in a murine model of glioma much better than virus loaded mesenchymal stem cells (MSC), both of which are tumor tropic carriers (Ahmed et al., 2011). This suggests that the trafficking efficacy of carriers might be closely linked to the similarity between the origin of the carrier and the malignancy. Substantial work needs to be done in understanding what causes different types of carriers to migrate to tissues differentially. With the results of some early clinical trials on the horizon, we will get a clearer picture of how efficacious NSCs are as carriers of therapeutics. Through the development of both increasingly specific therapeutics and better delivery systems, there is a hope that we will see dramatic enhancements in patient outcomes for this terrible disease.

Conflict of Interest

The authors declare no conflicts of interest.

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