Current treatments for advanced melanoma and introduction of a promising novel gene therapy for melanoma (Review)

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Abstract. Metastatic melanoma is a fatal form of skin cancer that has a tendency to proliferate more rapidly than any other solid tumor. Since 2010, treatment options for metastatic melanoma have been developed including chemotherapies, checkpoint inhibition immunotherapies, e.g., anti-cytotoxic T-lymphocyte antigen-4 (CTLA-4) and anti-programmed death-1 (PD-1), and molecular-targeted therapies, e.g., BRAF and MEK inhibitors. These treatments have shown not only high response rates yet also side-effects and limitations. Notwithstanding its limitations, stem cell therapy has emerged as a new auspicious therapy for various tumor types. Since stem cells possess the ability to serve as a novel vehicle for delivering therapeutic or suicide genes to primary or metastatic cancer sites, these cells can function as part of gene-directed enzyme prodrug therapy (GDEPT). This review focuses on introducing engineered neural stem cells (NSCs), which have tumor-tropic behavior that allows NSCs to selectively approach primary and invasive tumor foci, as a potential gene therapy for melanoma. Therapy using engineered NSCs with cytotoxic agents resulted in markedly reduced tumor volumes and significantly prolonged survival rates in preclinical models of various tumor types. This review elucidates current treatment options for metastatic melanoma and introduces a promising NSC therapy.

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1. Introduction

Melanoma is the most dangerous form of skin cancer. These invasive growths develop when unrepaired DNA damage causes mutations in skin cells resulting in prompt proliferation and the formation of malignant tumors. If melanoma is detected early, it can be easily cured with appropriate treatment such as surgical removal. However, metastatic melanoma often proves fatal and certain patients possess high-risk features for developing metastases. Melanoma can metastasize almost anywhere, from nearby tissues to distant major organs. The most typical metastatic sites are the lymph nodes, lungs, liver, brain and bones. Many academic reports have been published since 2010 on treatments for metastatic melanoma, from chemotherapies to molecular-targeted therapies.

Research concerning the application of stem cell-based therapies for cancer has recently emerged due to their potential function as a drug delivery vehicle for therapeutic genes directly to tumor sites. Stem cells, such as mesenchymal stem cells (MSCs) and neural stem cells (NSCs), are attractive delivery systems, as they are able to target tumor sites specifically due to the secretion of chemoattractant factors from tumors. Their ability to migrate and aggregate around the tumor at a high concentration gives them the potential as a vector of enzyme/prodrug gene in gene-directed enzyme prodrug therapy (GDEPT) of human cancers (1). This review discusses the current treatment options for metastatic melanoma patients and elucidates the possibility of applying NSC therapy for melanoma and justifying it with prior research on other stem cell-based therapies for melanoma.

2. Current treatments for advanced melanoma

Surgery. Identifying melanoma in its early stages is extremely important since patients with early stage melanoma can be surgically healed with relatively limited associated morbidity (2). Increasing patient survival can be accomplished

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by accompanying effective palliative management of local disease with removal of systemic, especially solitary lung, melanoma metastases (3). Of 144 patients who underwent surgical resection of non-regional melanoma metastases, 20% had a 5-year survival rate (4), and in a phase II trial conducted by the Southwest Oncology Group the overall 3- and 4-year survival rates of stage IV melanoma patients were 36 and 31%, respectively (5). Surgical tumor removal can prevent metastasis; however, surgical removal cannot be applied on microscopic metastases. Therefore, it must be used with other therapies such as surgical resection concomitant with systemic targeted therapies.

Radiation therapy. A total of 1-6% of patients with melanoma undergo radiation therapy in the USA. In particular, radiation therapy is used in patients with brain metastases as adjunct palliative therapy. Radiation therapy, in contrast to surgical management, has the benefit of potentially inducing an abscopal effect in which both the treated tumor and the non-irradiated site respond to the therapy (2). This abscopal effect is believed to be generated through immune system mediation, as radiation therapy can induce cross-priming in which released tumor antigens are expressed in MHC class I molecules by dendritic cells. Activated CD8$^+$ T cells can then migrate to far-off tumors and promote lysis (6).

Chemotherapy. Dacarbazine (DTIC) is well known as a primary chemotherapeutic treatment for metastatic melanoma. It is the first and only alkylating agent approved by the FDA with intravenous administration every 3-4 weeks at a dose of 800-1,000 mg/m^2 (7). DTIC functions by adding an alkyl group to the bases in DNA, which then prevents cells from replicating. As the sole agent of treatment, DTIC creates a partial response in up to 25% of melanomas and a complete response in ~5% (8,9). Oral delivery of the DTIC derivative, temozolamide, which showed a similar response rate in metastatic melanoma, was developed more recently. Temozolamide has the added ability to cross the blood-brain barrier, which led to it becoming a first-line therapy for brain metastases (10). Analysis of combinations of chemotherapies such as cisplatin, vinblastine, and DTIC has shown encouraging response rates, but they have failed to prolong overall survival (OS) when compared with the single agent DTIC (11,12).

Immunotherapy
Cytotoxic T-lymphocyte antigen-4 (CTLA-4). Activated T cells express CTLA-4. This acts as a negative regulator of T cells and helps preserve immunologic homeostasis. Ipilimumab is an antibody that blocks CTLA-4 from mediating T-cell downregulation and reinforces the antitumor effects of T cells (13). Response rates for ipilimumab alone range from 5 to 15% due to changes in the dosage and patient selection in clinical trials (14-17). A total of 1,861 patients were analyzed in 12 separate studies, and the median OS was 11.4 months (95% CI, 10.7-12.1 months) with a plateau at 22% in the survival curve around year 3 (18). Unfortunately, diarrhea, dermatitis, hepatitis, endocrinopathies, and immune-related adverse events accompanied the treatment (19). Clinical trials which focused on a combination of immunotherapy and chemotherapy such as ipilimumab and DTIC exhibited greater efficacy than

monotherapy. Patients treated with both ipilimumab and DTIC showed higher OS than those who were treated with only DTIC. The estimated survival rates for patients treated with a combination therapy of ipilimumab and DTIC were 47.3% for 1 year, 28.5% for 2 years, and 20.8% for 3 years compared to survival rates of 36.3, 17.9 and 12.2% for patients treated with DTIC monotherapy (14). Adverse effects of ipilimumab such as gastrointestinal perforations, diarrhea and colitis were less common in groups treated with a combination of ipilimumab and DTIC rather than ipilimumab alone at the same dose, but there were reports of elevated liver function values (14).

Programmed death-1 (PD-1). T cells upregulate a surface receptor called PD-1 at later stages of T-cell activation in contrast to CTLA-4, which is upregulated in the early stages of T-cell activation. PD-1 regulates the immune system by binding to T cells and attenuating their activity. Tumors are thought to avoid an immune response by upregulating PD-LI, a ligand of PD-1 (20,21). Therefore, preventing the PD-1 ligand from binding to the PD-1 receptor on tumor cells can recover the tumor-fighting function of immune cells. Nivolumab and pembrolizumab are antagonists of the PD-1 receptor that can disrupt the interaction of PD-1 and PD-L1. This disruption can allow T cells to proliferate, infiltrate the tumor and increase effector function (22). Pembrolizumab showed a 38% response rate with median survival of >7 months in initial clinical trials. In comparison with other melanoma treatments, the side-effects were significantly diminished (14,23). Nivolumab had parallel results for the treatment of ipilumumab-resistant or BRAF inhibitor and ipilimumab-resistant advanced melanoma. With nivolumab, 31.7% of patients had an objective response compared to 10.6% of patients who were treated with the investigator's choice of chemotherapy (ICC) (24). Adopting a combination therapy of nivolumab and ipilimumab has shown the highest response rates. Using these therapies simultaneously in phase I and II trials demonstrated a 53-61% response rate with >80% tumor reduction in all responding patients (25,26). This result shows a synergistic effect between CTLA-4 and PD-1 inhibition and a recent report [Larkin *et al* (2015)] showed that the median progression-free survival (PFS) of the combination therapy was 11.5 months (95% CI, 8.9-16.7) compared with 2.9 months (95% CI, 2.8-3.4) with ipilimumab alone and 6.9 months (95% CI, 4.3-9.5) with nivolumab alone (27). Vitiligo, colitis, hepatitis, hypophysitis, and thyroiditis are adverse events of nivolumab, but they appear less often compared to the treatment with a CTLA-4 antagonist. In addition, inflammatory pneumonitis along with a dry cough, dyspnea, and ground opacities are unique to PD-1 blockade and are potentially lethal (28).

Molecular-targeted therapy
BRAF inhibitor. The BRAF gene encodes a serine/threonine kinase that is engaged in the mitogen-activated protein kinase (MAPK)/ERK signaling pathway (29). The MAPK/ERK signaling pathway is associated in transferring signals for cellular proliferation and survival from the cell surface to the nucleus, and ~50% of cutaneous melanomas are caused by a mutation in the BRAF oncogene, which leads to fundamental activation of the MAPK signaling pathway and uncontrolled cellular proliferation (30,31). Vemurafenib and dabrafenib are potent BRAF inhibitors with distinct antitumor

effects specific to melanoma cell lines with the BRAF V600E and V600E/K mutations (32-35). In its initials trials, treatment with vemurafenib induced complete or partial tumor regression in 81% of patients with melanoma containing the V600E BRAF mutation (32). Vemurafenib received approval for BRAF inhibitor monotherapy in 2011. Dabrafenib is another BRAF-targeted therapy for melanoma which functions as a reversible ATP-competitive inhibitor for BRAF and was approved in March 2013 (31). Median PFS for vemurafenib is 6.8 months compared to 5.1 months for dabrafenib, which signifies that dabrafenib is not more effective than vemurfaneib monotherapy (34,36). However, a study showed that dabrafenib demonstrated efficacy for patients with brain metastases and remains an effective therapeutic option for this particular population (37). Vemurafenib showed favorable *in vitro* and *in vivo* results and a 69% objective response rate in phase I clinical trials (38,39). As clinical trials proceeded to later phases, however, 90% of patients gained resistance and showed disease progression within 9 months.

Arthralgia, fatigue, aminotransferase elevation, nausea, vomiting and decreased kidney function were reported as general side-effects of vemurafenib, and ~11% of patients administered dabrafenib reported pyrexia as a side-effect (13,34).

BRAF resistance. Repeated exposure to mutant BRAF inhibitors can alter not only the RAS-RAF-MEK-ERK signaling pathway but also several other kinase pathways (36). As a result, expression levels of RAS, CRAF and MEK were increased due to ERK pathway reactivation (40,41). ERK signaling reactivation is driven by the amplification or alternative splicing of BRAF causing BRAF dimerization that prevents inhibitors from binding to BRAF V600E monomers (42,43). For example, activation of the PI3K/AKT signaling pathway promotes BRAF inhibitor resistance in melanoma and is therefore a form of adaptive resistance (44). Changes in the tumor microenvironment caused by increased levels of growth factors such as hepatocyte growth factor (HGF) can be another mechanism for BRAF inhibitor resistance and were found to be linked to poor clinical outcomes (45,46). However, changes in tumor microenvironment are not hypothesized to be the primary cause of drug resistance, but they are considered to be a secondary contributor which could be a targetable option for preventing adaptive resistance in melanoma tumors (47).

MEK inhibitor. While direct targeting of mutated oncogenic BRAF has been successful for those with mutated BRAF metastatic melanoma, blocking MEK, a protein located downstream of BRAF in the MAPK signaling pathway, showed remarkable success as well. Compared to oncogenic BRAF mutations, oncogenic MEK mutations are less common in melanoma. However, because of BRAF inhibitor resistance, targeting downstream of BRAF for therapeutic efficacy has become a research topic of interest (13,31). The common MEK mutation C121S accelerates melanoma growth and confers resistance to BRAF V600E mutant melanoma cells to vemurafenib. C121S creates an active kinase that allows for activation of downstream ERK without upstream activation by BRAF (48). A MEK inhibitor called trametinib has been FDA approved as a single agent for melanoma patients with BRAF V600E or V600K mutations as of June 2013 (13). Trametinib impedes the progression of advanced melanoma, especially in BRAF-mutant patients (17,49). Trametinib showed a 33% response rate for BRAF mutants with 5.6 months of median PFS in recent clinical trials compared to a 10% response rate for BRAF wild-type tumors (50,51). Although trametinib showed more improvement in PFS and OS compared with chemotherapy, the objective response rate was still lower than that of BRAF inhibitors (13). Furthermore, trametinib produced side-effects including diarrhea, peripheral edema, hypertension and fatigue, which are typical of other MEK inhibitors as well (52). Many resistance pathways found in other treatments, especially BRAF inhibitors, depend upon MEK signaling. Thus, MEK inhibition by trametinib in combination with other treatments was able to increase their potential as therapeutic agents and attenuate resistance in clinical trials (50,51).

Combination-targeted therapy. BRAF resistance from BRAF kinase inhibitors is generated by reactivation of the MAPK pathway. In order to solve this problem, Flaherty *et al* performed a combined treatment with a selective BRAF inhibitor, dabrafenib, and a selective MEK inhibitor, trametinib, in phase I and II trials (53). Vemurafenib was found to inhibit MAPK signaling in melanoma patients with the BRAF V600E mutation and produce prolonged survival and PFS in randomized phase III trials in patients who had not previously received melanoma treatments. Trametinib restricts MEK, a protein downstream of BRAF in the MAPK pathway, and it showed an improvement in progression-free survival and OS in BRAF V600E and V600K mutant melanomas. Rapid reactivation of the MAPK signaling pathway has been related to BRAF inhibitor resistance in preclinical models, but stimulation of cell death in BRAF V600 mutant melanoma requires complete inhibition of the MAPK pathway. This can be attained by combining a BRAF inhibitor with an MEK inhibitor (53). The median OS for combined treatment with trametinib and dabrafenib in a multicenter, double-blind, phase III randomized controlled trial on BRAF-mutant melanoma patients was 25.1 months (95% CI, 19.2- not reached) and 18.7 months (15.2-23.7) for the dabrafenib only-treated BRAF-mutant melanoma patients [hazard ratio (HR), 0.71; 95% CI, 0.55-0.92; p=0.0107]. Median PFS for the dabrafenib and trametinib-combined therapy was 11.0 months (95% CI, 8.0-13.9) and for the dabrafenib only-treated group this value was 8.8 months (5.5-9.3) (HR, 0.67; 95% CI, 0.53-0.84; p=0.0004) (54). Flaherty *et al* examined the adverse side-effects of combination therapy with dabrafenib and trametinib. Patients who received both dabrafenib and trametinib treatment had more constant and severe pyrexia and chills compared to those who had only dabrafenib treatment. They also had more persistent gastrointestinal toxic effects, such as nausea and vomiting, but the majority were grade 1 or 2 events (53).

3. A promising novel therapy for cancer - neural stem cell therapy

Neural stem cells. NSCs are self-renewing created by the differentiation of embryonic tissue and generate the neurons and glia of the developing brain. NSCs can be isolated, genetically engineered and differentiated *in vitro* and reinstated into the central nervous system (CNS). NSCs have potential for use

in cell replacement therapies in various neurologic disorders as has been shown in several academic reports (55,56). NSCs can be defined as cells that self-renew constantly and have the potential to form intermediate and mature cells of neuronal and glial lineages (57). From the year 2000 onward, there have been many reports concerning the adoption of NSCs as a drug delivery vehicle specific to brain sites instead of solely cell replacement. NSCs were found to appear near metastatic tumor cells far from where they were transplanted into animal models of brain neoplasia in these reports. This opens the possibility to track down and destroy malignant cells by manufacturing NSCs with chemotherapeutic qualities (58-60). NSCs have the unique ability to integrate into the host's brain without interfering with normal functions and can proliferate for long periods (61). This uniqueness could allow NSCs to be suitable as therapeutic delivery vehicles for CNS disorders. In addition, their tropic migration towards neoplasms is another favorable characteristic for their use as vehicles for targeted delivery (55). Benedetti *et al* and Aboody *et al* demonstrated that the progression of cancer xenografts was suppressed by the cytotoxic effects of NSCs that were manufactured with antitumor gene products (58,60). These studies opened the doors to the potential of drug-equipped NSCs as a tumor-homing therapy. NSCs migrate not only to injured areas but also towards tumor foci. The tumor-tropic homing of NSCs is directed by chemoattractants produced by cells in the normal brain wounded by tumor growth or directly released from glioblastoma multiforme (GBM) cells (62,63). In hypoxic conditions, GBM cells upregulate the expression of numerous pro-angiogenic factors and chemoattractants. The relevance of hypoxia in the tumor-tropic migration of NSCs towards GBM was demonstrated through several siRNA-mediated knockdowns. The expression of the chemoattractant factor stromal cell-derived factor-1 (SDF-1), uPA and vascular endothelial growth factor (VEGF) was reduced with knockdown of HIG-α in GBM cells, which led to no tumor-tropic migration of NSCs (62). More cytokines, growth factors, and receptors have been addressed such as (SCF)/c-Kit (64), monocyte chemoattractant protein-1 (MCP-1)/CCL2 (65), Annexin A2 (66), HGF/c-Met (67) and HMGB1/RAGE (68) for arbitrating the tumor-tropic migration of NSCs. Engineered NSCs could be designed to express a plurality of receptors, so they can be deployed wherever chemotactic signals are emitted from brain pathologies. Various groups have revealed the potential of migrating towards not only tumors of glial origin but also metastatic breast cancer and melanoma foci in the brain (69-71). Due to their intrinsic migratory and tumor-tropic properties, NSCs epitomize a novel and potentially efficacious approach for the treatment of invasive tumors.

Gene-directed enzyme prodrug therapy of human cancer. Conventional treatments of cancer are impeded by their inadequacy in being selective and specific to *de novo* tumors. They harm normal and healthy tissues by their toxicity. HB1.F3 cells, a parental cell line of the HB1.F3.CD/CE cell line, show migration to subcutaneous xenografts of various solid tumors such as prostate cancer, breast cancer, melanoma, glioma and neuroblastoma. This suggests that these cell lines do not show tissue-specific characteristics for therapeutic use (70).

GDEPT is a promising approach for advancing the selectivity of conventional chemotherapeutics. GDEPT improves selectivity by delivering 'suicide' genes such as cytosine deaminase (CD), carboxylesterase (CE), and herpes simplex virus type 1 thymidine kinase (HSV1-tk), to cancer cells, which lets them convert non- or low-cytotoxic prodrugs to cytotoxic drugs (58,72,73). Using GDEPT allows human tumors to be selectively targeted and specifically treated to increase efficacy and diminish the side-effects of biological drugs (74). For example, CD converts 5-fluorocytosine (5-FC), a non-toxic drug, to 5-fluorouracil (5-FU), a toxic agent, CE converts CPT-11 to SN-38, and HSV1-tk converts GCV to an active metabolite. An essential aspect of GDEPT is a foreign enzyme expressed only at the tumor site where it is able to shift a prodrug into its cytotoxic metabolite *in vivo* (58). The therapeutic efficacy of a polymerase chain reaction (PCR) vector which conveyed a suicide gene, yeast CD, that converts the prodrug 5-FC to the cytotoxic 5-FU was exhibited after delivery by infusion into the regional circulation in a multifocal hepatic metastasis model of colon cancer (75). A noticeable boost in apoptotic cells and a decrease in proliferated cells in human breast cancer cell lines was detected when combined treatment was used with the CD/5-FC suicide system and hTNFα expression (76).

Tropism of neural stem/progenitor cells to human cancers. Selective penetration to tumor sites is the primary handicap that current gene therapy strategies are confronting, but this can be overcome by using NSCs. NSCs are able to serve as a delivery vehicle to target and propagate therapeutic gene products over tumor sites. The human NSC line HB1.F3.CD was implanted intracranially at distant sites from the tumor, and the NSCs selectively migrated to the GBM tumor mass while bypassing normal tissue which resulted in 80-85% reduction in tumor volume after injection of the prodrug 5-FC (69,77,78). NSCs are assumed to have a bystander effect through their selectively eliminating behavior against dividing tumor cells wherein toxic prodrugs and their metabolites circulate across gap junctions and interstitial space to surrounding cells (74). Although the selective migration towards tumor sites of HB1.F3 parental cells, the HB1.F3.CD/CE cell line and other stem/progenitor cells has not been fully explained, biological factors such as SDF-1, scatter factor (SCF; HGF), VEGF and MCP-1 expressed in tumor cells seem to participate in chemotaxis to human tumors (55,64,68,79-83). Adopting the tumor-tropic behavior of NSCs could lead to significant utility for the treatment of a variety of metastatic tumors.

Alternative stem cell-based therapies for melanoma treatment. Among many types of stem cells, MSCs have emerged as a potential transporter for not only regenerative medicine but also cancer therapy. There have been several studies suggesting that MSCs are able to migrate to both primary and metastatic tumor sites through associations with various chemokines and cytokines (1). Similar to NSCs, MSCs can track specifically to tumor sites via chemokines and cytokines emitted from tumors (84-87). There is a large body of research concerning the application of MSCs as carriers of anticancer agents for melanoma treatments. For example, bone marrow-derived MSCs engineered to carry the P450 gene showed the ability

Table I. Engineered stem cells for therapeutic efficacy in preclinical models of different tumor types.

Tumor type (cell line)	NSC type (prodrug)	Tumor volume[a] (%)	Survival rate	Ref.
Breast cancer (MDA-MB-231/luc)	HB1.F3.CD (5-FC)	50	30% (13 weeks)	(92)
	HB1.F3.CD.IFN-β (5-FC)	50	80% (14 weeks)	
Endometrial cancer (Ishikawa)	HB1.F3.CD (5-FC)	50	ND[b]	(93)
	HB1.F3.CD.IFN-β (5-FC)	60	ND[b]	
Human colorectal cancer (HT-29)	HB1.F3.CD (5-FC)	56	50% (11 weeks)	(94)
	HB1.F3.CD.IFN-β (5-FC)	76	70% (11 weeks)	
Pancreatic cancer (PANC-1)	HB1.F3.CD (5-FC)	50	ND[b]	(95)
	HB1.F3.CD.IFN-β (5-FC)	50	ND[b]	
Lung cancer (A549)	HB1.F3.CE (CPT-11)	80	ND[b]	(96)

[a]Tumor volume is shown in a ratio of negative control to treatment group. [b]ND, no data are shown. NSC, neural stem cell; 5-FC, 5-fluorocytosine.
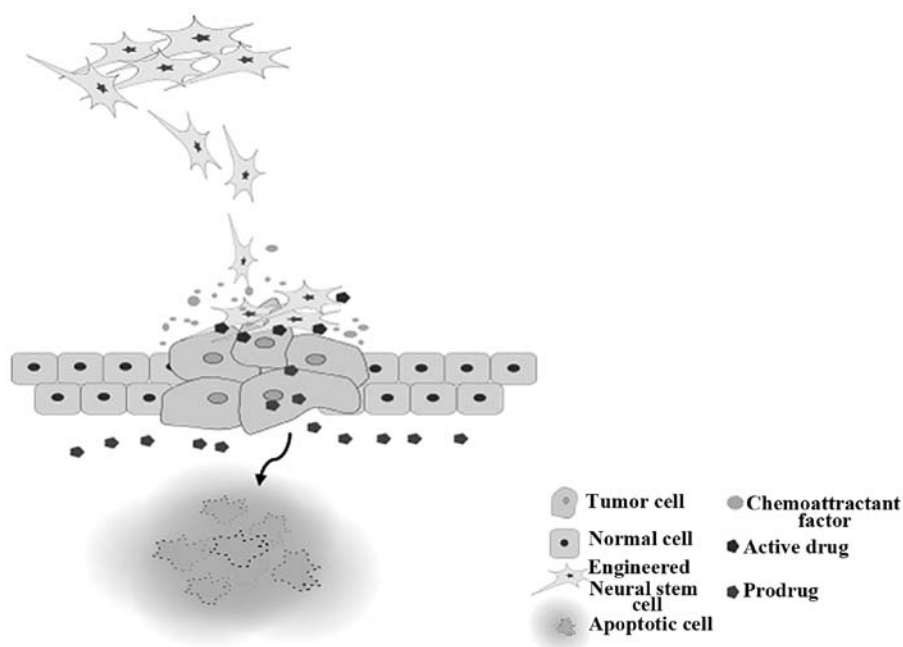

Figure 1. Selective cytotoxic effect of engineered neural stem cells (NSCs). Selective behavior of NSCs may be achieved by chemoattractant factors emitted by tumor cells. NSCs engineered to convey suicide genes can migrate to tumor sites and convert a non-toxic prodrug to a toxic active drug, which leads tumor cells to undergo apoptosis. The tumor-tropism of engineered NSCs allows them to target only tumor cells increasing their efficacy and decreasing side-effects.

to inhibit the growth of malignant melanoma *in vitro* and *in vivo* by reinforcing the expression of CYP2E1 (88). A study by Jing *et al* used adipose tissue-derived mesenchymal stromal cells (AT-MSCs) as a carrier to deliver enhanced expression of TRAIL protein for impeding melanoma growth. TRAIL protein induced apoptosis by readjusting the expression of members of the PI3K-AKT signaling pathway (89). Seo *et al* demonstrated the antitumor effect of engineered canine AT-MSC (cAT-MSC)-producing interferon-β with cisplatin in mouse melanoma models. The combination of cAT-MSC-IFN-β and cisplatin had more compelling results than the cisplatin-alone group in inhibiting the growth of melanoma and increasing the survival rate (90). Tyciakova *et al* used engineered AT-MSC-secreting TNFα protein to assess

its therapeutic effect on melanoma. AT-MSC-TNFα restrained melanoma cells from growth *in vitro* by inducing apoptosis via activating caspase-3/7 and inhibited the tumor mass up to 97.5% (91). All these studies suggest that stem cells are satisfactory as a carrier of both anticancer drugs and genes for targeting cancers. Overall, the data obtained from alternative stem cell-based therapies on melanoma propose the feasibility of NSCs as a delivery system for targeted agents in the treatment of melanoma.

4. Conclusions

As we learn more about the mechanisms of melanoma, treatment has been revolutionized. The advancement of immunotherapies

and targeted therapies has significantly improved clinical results. However, although there are currently more wide-ranging treatment options than in the past, it has become apparent that monotherapy will likely be unsuccessful due to the aggressiveness and hypermutable nature of melanoma tumors. Thus far, combination therapy has produced the most convincing clinical results. Although both immunotherapy and targeted therapies have conspicuous advantages and disadvantages, preclinical results show that the combination of these treatments could enhance patient outcomes. However, related data are inadequate to make a concrete determination, as the data of patients treated with combination therapy are limited. The toxicity and resistance issues plaguing many existing treatments must also be carefully considered with combination therapy. Therefore, the ultimate efficacy of combination therapies remains unclear until further data are gathered.

The common obstacle that current melanoma treatment options confront is damage to other tissues. This issue has placed patients in situations where whether to continue their treatment or not has been a serious consideration for maximizing their chances of survival. However, a parental cell line of HB1.F3.CD/CE has been demonstrated to exhibit migratory behavior to subcutaneous xenografts of various solid tumors in the prostate and breast as well as melanoma, glioma, and neuroblastoma (Fig. 1). We can interpret that engineered NSCs with suicide genes can be used to selectively target not only melanoma but also tumors that have already metastasized to other sites without damaging normal tissues for therapeutic use, as demonstrated in Table I. Although, to date, research is lacking regarding the use of engineered NSCs for melanoma, data from other stem cell-based therapies on melanoma and the features of NSCs indicate that NSC therapy could be the next paradigm in gene therapy for melanoma and other cancers in preclinical and clinical cases. Thus, their potential as a specialized delivery vehicle should be explored in future studies.

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