

# Melanoma stem cells: the past, present and future

## Abstract

Metastatic melanoma is a cancer that is notoriously difficult to treat due to its ability to form resistance to various treatment regimens. Cancer stem cells represent a population of tumor cells capable of self-renewal and differentiation, capable of maintaining the tumor, and capable of resisting treatment. Melanoma stem cells have also been identified with increasing amounts of information being elucidated about these cells over the past decade. Therapeutic targeting of stem cells will be a key component in the fight against malignant melanoma and other cancers in the future.

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## Introduction

Normal adult stem cells are characterized by their ability to self-renew, as well as their ability to differentiate into various mature cell types. Cancer stem cells were first recognized by Bonnet et al, who showed a sub-portion of acute myelogenous leukemia (AML) stem cells could be identified and separated from AML cells in patients. This subset of AML cells were the only cells capable of transferring AML from the human patients to studied mice.<sup>1</sup> The hypothesis of the existence of cancer stem cells gained more attention around 2001 when Reya et al pushed the notion that cancer stem cells are composed of a subset fraction of tumor cells that have the ability to maintain the tumor through self-renewal, conferring drug resistance, and inducing tumor relapse.<sup>2</sup> These cancer stem cells have similar physiologic properties to normal adult stem cells, like self-renewal and differentiation. Normal stem cells had been shown to be resistant to cytotoxic agents compared to mature cell types, which is explained by anti-apoptotic mechanisms,<sup>3</sup> quiescence,<sup>4</sup> and high expression levels of ATP-binding cassette (ABC) transporters.<sup>5</sup> Thus, the existence of cancer stem cells explains the reason why many treatments for metastatic tumors ultimately fail. Current treatments like chemotherapy and radiation can shrink, but not cure metastatic tumors. Frequently, these treatments do indeed target the bulk of tumor cells in the human body, but often, the drug therapy is unable to kill the cancer stem cells (due to inherited and/or acquired resistance), and thus the tumor can easily grow back. In recent years, cancer stem cells have been identified and isolated by characteristics of normal stem cells, like using tissue specific CD markers (The cluster of differentiation) and ABC transporter proteins.<sup>6</sup> Research about targeted therapy in regard to these cancer stem cells has come in full swing over the past decade.

## Melanoma stem cells

Melanoma is a heterogenous skin cancer arising from melanocytes and is notorious for forming resistance to chemotherapy and targeted therapy in its advanced stages. One theory to explain this heterogeneity is the cancer stem cell hypothesis. As cancer stem cells have been defined by their ability to self-renew and differentiate, melanoma stem cells (MSCs)-also called malignant melanoma initiating cells-also followed this definition. Fang et al in 2005 were the first to report the

presence of melanoma stem cells. These MSCs were enriched in the CD20 surface marker, normally a marker of mature B lymphocytes. These CD20+ melanoma cells were capable of self-renewal and differentiation.<sup>7</sup> In 2008, Schatton et al demonstrated ABCB5, an ABC transporter protein known to confer drug resistance, as the first functional putative biomarker for melanoma stem cells.<sup>8</sup> Many other markers were discovered for MSCs after this, including CD133, CD271 and ALDH.<sup>9,10</sup> However, more research and exploration is required to establish exclusive markers for MSCs.

MSCs are unique in their immune evasion techniques. MSCs that express ABCB5 are associated with decreased expression of melanoma antigen recognized by T cells-1 (MART-1), which is associated with melanocyte differentiation and T cell recognition, in order to evade host T-cell recognition.<sup>11</sup> MSCs also evade the immune system with altered expression of major histocompatibility complex and inhibition of interleukin-2 (IL-2), two components critical in host immunity.<sup>11</sup>

Considering the knowledge gained about MSCs and their existence, there are multiple future outlets to explore in regard to the treatment of melanoma and stem cells. First, melanoma stem cell specific markers can be detectable targets using monoclonal antibodies. Since MSCs express CD20, rituximab, a CD20 antibody therapy, has been attempted in clinical trials to treat melanoma, producing regression in chemotherapy-refractory melanoma.<sup>12</sup> Similarly, a monoclonal antibody against ABCB5+ MSCs in mouse models showed tumor inhibitory effects.<sup>8</sup>

Given that MSCs block IL-2 as a mechanism of immune evasion, future therapy can focus on regulators of the immune response. For example, cytotoxic T-lymphocyte antigen-4 (CTLA-4) is a receptor associated with the ligand B7-2 upregulated by ABCB5 MSCs, and combined, they negatively regulate host T-cell activation.<sup>13</sup> Indeed, anti-CTLA4 monoclonal antibodies, ipilimumab and tremelimumab have shown promise in clinical trials<sup>11,14</sup> in patients with metastatic melanoma. Tuccito et al.<sup>15</sup> were able to demonstrate another effective means to modifying the immunologic tumor microenvironment. They demonstrated that interleukin-6 (an inflammatory cytokine) released from differentiated melanoma cells reduced MSC self-renewal and instead induced differentiation. Interleukin-10 (an anti-inflammatory

cytokine) release on the other hand, promoted MSC self-renewal. By silencing interleukin-10 by blocking the IL-10 receptor, Tuccito et al.<sup>15</sup> were able to sensitize MSCs to interleukin-6 and thus induce MSC differentiation. Through these cytokine manipulations, they were able to decrease MSC self-renewal capacity, and instead differentiate stem cells to a more easily targeted phenotype.<sup>15</sup>

Du et al have recently shown how to use stem cells as an ally (rather than an enemy) in treatment of metastatic melanoma to the brain. In the mouse model, they successfully demonstrated the utility of mesenchymal stem cells to carry oncolytic herpes simplex virus through intracarotid administration to metastatic brain lesions and deliver the oncolytic viruses. This is important in the future treatment of metastatic melanoma because of the paucity of options and high mortality associated with metastatic melanoma to the brain.<sup>16</sup>

## Conclusion

Malignant melanoma is a difficult to treat cancer due to its heterogeneous subpopulations of cells. The awareness of the existence of melanoma stem cells will be critical in the future to combat melanoma. Future therapy can be targeted at melanoma stem cell biomarkers, microenvironment, or even using stem cells as a treatment option themselves. Nevertheless, much more research in melanoma and stem cells will be necessary to fully add clarity to treatment plans.

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## Conflicts of interest

Authors declare no conflicts of interest.

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