Notch1-MAPK Signaling Axis is Essential in CD133+ Melanoma Initiating Cells

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Commentary

Human malignant melanoma is highly aggressive and metastatic in nature and exhibits phenotypic plasticity. Melanoma has multiple phenotypically distinct subpopulations which involved in tumor progression and markedly resistant to conventional therapy. Some of the melanoma subpopulation exhibits stem cells feature and defined as cancer stem cells (CSCs) or tumor initiating cells (TICs). Identification and characterization of CSCs in melanoma may have therapeutic implication for combating melanoma progression. In recent study, we have identified that CD133+ subpopulation of melanoma potentially involved in tumor initiation, metastasis, epithelial to mesenchymal transition (EMT) and angiogenesis. Genetic and pharmacological screening revealed that functional properties of CSCs in melanoma cells are regulated by Notch1-MAPK signaling axis. Andrographolide (herbal product) abrogates Notch1-MAPK pathway in CD133+ cells that leads to attenuation of melanoma progression, metastasis and angiogenesis.

The study of tumor initiating cells provides a potential explanation of tumor aggressiveness, drug resistant and distant metastasis [1,2]. Several reports showed that CD133, CD20, CD271, ABCG2 and ABCB5 act as a potential marker to characterize CSCs in melanoma [3,4]. However, the molecular mechanism between cancer stem cells markers and with their associated functions remains to be elucidated. Studies showed that CD133 has potential to act as an important marker to characterize melanoma initiating cells [5,6]. In our recent study [7], we have identified that CD133+ subpopulation in melanoma exhibits distinct molecular feature compared with CD133- cells. CD133+ cells showed higher expression of Oct3/4 and Nanog and exhibit self-renewal properties under in vitro and in vivo conditions which indicates a characteristic feature of CSCs. These cells are highly tumorigenic in nature and maintain long-term tumor growth. Our in vitro and in vivo data showed that CD133+ subpopulation exhibits EMT, metastasis and angiogenesis in melanoma. Previous studies showed that acquisition of chemoresistant is associated with high expression of multidrug resistant (MDR) protein, IL-8 and VEGF [3,8,9]. Our data indicates that CD133+ subpopulation exhibits higher percentage of SP phenotypes which probably associated with chemoresistance against DTIC, Dox, Dabrafenib and Trametinib [7]. Osteopontin, a cytokine has multiple role in tumor progression and metastasis [10,11]. The study by Pietras et al. have showed that osteopontin (OPN)-CD44 signaling axis in glioma niche enhances CSCs traits and promotes aggressive tumor growth [12]. OPN also promotes CSCs phenotypes in hepatocellular carcinoma cells via integrin-NF-kB HIF-1a signaling [13]. Additionally, Kumar et al. have observed that stromal OPN induces melanoma progression through enrichment of SP phenotypes [14]. Angiogenesis is an important phenomenon for the tumor development and metastasis [15]. Our recent data showed that CD133+ cells exhibit enhance expression of vascular endothelial growth factor (VEGF) and robust angiogenesis either through trans-differentiation into endothelial-like cells or recruiting neo-vascularisation [7]. We also observed that CD133+ cells exhibit the upregulation of mesenchymal markers Slug, Snail and N-cadherin and downregulation of epithelial markers E-cadherin which is an indication of the EMT phenotype. Additionally, CD133+ cells are robustly metastasized to the lung as compared to CD133- cells [7].

Several studies indicate that CSCs are responsible for limited tumor response against conventional treatment due to specific intracellular molecular properties [16]. Thus identification of signaling pathway by which CSCs exhibit protective mechanisms against conventional therapy is essential at this moment. The molecular characterization in our recent studies revealed that Notch1 and MAPK signaling pathway

**Figure 1:** Melanoma is heterogeneous in nature. The CD133+ melanoma cells have both tumor initiating and self-renewal ability. The Notch1-p38-MAPK signaling axis regulates tumor formation properties of the CD133+ cells. Andrographolide (Andro) is able to attenuate this signaling axis in CD133+ cells that leads to abrogation in melanoma progression and metastasis.
is predominantly active in CD133+ compared with CD133− cells [7]. Our genetic and pharmacological experimental analysis showed that Notch1 intracellular domain (NICD1) transcriptionally regulates CD133 expression which activates p38-MAPK pathway. Activation of p-38 MAPK pathway leads to AP-1-DNA binding and regulates angiogenesis and metastasis associated genes such as VEGF and MMPs (Figure 1). Several drugs including DTIC, Trametinib and Dabrafenib widely used as chemotherapeutic agents for the treatment of melanoma patients. Moreover, these agents exhibit several side effects and drug resistance [8,17,18]. Studies showed that Andrographolide (Andro), which is derived from Andrographis paniculata, act as an anticancer agent with less side effect and is able to target CSCs in multiple myeloma [19-21]. Our data demonstrate that Andro is able to eliminate CD133+ cells from melanoma and reduces the tumor growth. Mechanistic study revealed that Andro inhibits Notch1-MAPK signaling axis that leads to attenuation of CD133+ cells-mediated melanoma progression, metastasis and angiogenesis (Figure 1).

Conclusion

Our results identify the molecular mechanism of CSCs that help in the metastasis, angiogenesis and tumor progression. Targeting Notch1-MAPK signaling axis attenuates CD133+ cells-mediated melanoma progression. Thus, our study has addressed an important gap with CSCs markers and their associated function in melanoma model. In future, we need to find potential therapeutic targets and agents for the prevention or treatment of CSCs mediated melanoma progression.

Conflicts of Interest

The authors disclose no potential conflicts of interest.

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References