Review-Derleme

CD133 and CD44 expression patterns in gliomas and meningiomas

Glioma ve meningiomalarda CD133 ve CD44 ekspresyon paternleri

Baki Serdar Albayrak*, Özgür İsmailoğlu, Serdar Kabataş, Cem Yılmaz, Erdinç Civelek, Çağrı Gülümser

Department of Neurosurgery (Assist. Prof. S. B. Albayrak, MD, Assist. Prof. Ö. İsmailoğlu, MD), Süleyman Demirel University School of Medicine, TR-32260 Isparta, Department of Neurosurgery (S. Kabataş, MD), Başkent University Hospital, TR-34662 İstanbul, Department of Neurosurgery (Assist. Prof. C. Yılmaz, MD, E. Civelek, MD), Başkent University Hospital, TR-06810 Ankara, Department of Obstetrics and Gynecology (Ç. Gülümser, MD), Nallıhan State Hospital, TR-06920 Ankara

Abstract

CD133 and CD44 are widely expressed cell-surface markers in glioblastoma multiforme (GBM) and meningiomas respectively. Recent molecular studies revealed that CD133-positive GBM cells have cancer stem cell features with self-renewal and self-recapulating capacity. Similarly, it is also known that CD44 is expressed differentially on various meningioma subtypes and several studies in the literature reported that CD44 expression is correlated with the invasiveness of meningiomas. In this context, we aimed to highlight the expression patterns of CD133 and CD44 and their implications with the potential cancer stem cells in glioblastoma multiforme (GBM) and meningiomas, respectively.

Keywords: Glioma, meningioma, cancer stem cell, CD133, CD44

Özet

CD133 ve CD44 sırasıyla glioblastoma multiforme (GBM) ve meningiomlarda geniş ölçüde tespit edilen hücre yüzey işaret molekülleridir. Yakın zamandaki moleküler çalışmalar CD133 müspet GBM hücrelerinin kanser kök hücrelerinin sahip olduğu düşünülen 'kendini yenileme ve yineleme' özelliklerine sahip olduklarını göstermiştir. Benzer şekilde, CD44 yüzey işaretinin de değişik meningioma alttiplerinde olduğu bilinmektedir ve birkaç çalışmada CD44 miktarıyla meningioma invazyonu arasında ilişki olduğu bildirilmiştir. Bu bağlamda, CD133 ve CD44 hücre yüzey işaret moleküllerinin sırasıyla GBM ve meningiomlardaki sunulma biçimlerini ve bu moleküllerin potansiyel kanser kök hücreleriyle olan ilişkilerini vurgulamayı amaçladık.

Anahtar sözcükler: Gliom, meningiom, kanser kök hücresi, CD133, CD44

*Corresponding author:

Baki Serdar Albayrak, MD, Nöroşirurji Anabilim Dalı, Süleyman Demirel Üniversitesi Tıp Fakültesi, TR-32260 Isparta. E-posta: serdarbaki@gmail.com

Introduction

The CD133 (a.k.a., Prominin I) a cell-surface antigen is a 97 kDa glycoprotein which binds to the cell membrane cholesterol, and is associated with a particular membrane microdomain in a cholesterol-dependent manner [1, 2]. Even though the exact biological function of CD133 is not known, it has been shown as a marker for stem and progenitor cells including neural and embryonic stem cells as well as hematopoietic stem and progenitor cells in both humans and mice. CD133 was also shown to be expressed in

cancers, including some leukemias and brain tumors, mostly in gliomas and medulloblastomas (Table 1) [1, 3, 4].

Table 1. Cell surface markers of cancer stem cells in various solid tumors.

Glioma	CD133+, A2B5+
Meningiomas	CD44+
Medullablastoma	CD133
Breast	CD133+, CD44+, CD24-
Ovarian	CD44+, CD24+
Prostate	CD44+, CD24+
Melanoma	CD133+, CD44+, CD24+, CD20+, CD166+

CD44 is a widely distributed cell surface marker and cell adhesion molecule. Suzuki et al. [5] demonstrated the differential expression of CD44 in various meningioma subtypes. Only the secretory meningiomas appeared to express variant forms of CD44 favoring tumor cell differentiation to epithelial type, whereas meningothelial, fibrous, and malignant meningiomas express the standard form of CD44.

Related literature review and discussion

GBM and meningiomas constitute more than half of the primary brain tumors. The GBM has still no definitive cure and has a dismal prognosis with the survival times ranging between 45 to 71 weeks following radical surgical resection, radiotherapy with/without chemotherapy [5-7]. On the other hand, meningiomas are mostly benign neuro-ectodermal tumors and are curable by surgical resection alone in most instances. However, the portion of atypical or malignant meningiomas did exhibit marked increase and in turn the recurrence rate of meningiomas overall has shown significant rise [8-10]. This can be partly explained by the introduction of more sophisticated molecular and genetic assays as to specify each meningioma tumor cell population more specifically at the molecular level. Cancer stem cells in gliomas were first proposed by Dirks et al. [11] a decade ago and it was shown that CD133-positive glioma cells in the glioma cell-population has the self-renewal and self-propagating capacity and they appear as the "chief cells" among all tumors cells. However, the exact biological function of CD133 is not discovered yet currently. Likewise, it is known that CD44, another cell surface marker is structurally integrated with merlin protein in the cell membranes of meningioma cells and its hyper-expression may be associated with the invasiveness and anaplasia of meningiomas [12, 13].

Expression of CD133 in glioblastoma multiforme (GBM)

GBMs are heterogenous tumors with a small subset of cancer stem cells, a.k.a tumor-initiating cells, which have a high tumor forming potential. These cancer stem cells are similar to the normal stem cells which express CD133, characteristic of neural stem cells and posses the self-renewal potential. Numerous studies have demonstrated that only CD133-positive cancer cells of GBM have tumor-initiating potential. Furthermore, cancer stem cells derived from glioblastoma are capable of recapitulating original tumors when transplanted into nude mice. However, recent studies have shown that even CD133-negative GBM cells have also the tumor-initiating capacity and one particular study has revealed that CD133-negative GBM cells have lower proliferation capacity than that of CD 133-positive GBM cells [14]. Nevertheless, it is evident that CD133 is a cell surface marker which plays an intricate role in the GBM initiation and progression. These findings raise a question if GBMs can be cured by targeting and eradicating CD133-positive cancer stem cells (CSCs), which are only the small portion of GBM cells. However, GBMs are highly heterogenous tumors with numerous genetic aberrations therefore more than one single universal CSC may exist within each GBM tumor cell population.

Expression of CD44 in meningiomas

Several studies in the literature revealed convincing evidence that the over-expression of CD44 was often associated with increased migration ability and anaplasia in meningioma cells. Sainio et al. [15] demonstrated the co-localization of NF2 gene encoded merlin protein with CD44 and pointed out the interaction of CD44 and cytoskeleton via ezrin, radixin, and moesin proteins which are structural relatives of merlin protein. Similarly, Morrison et al. [16] presented additional evidence regarding the role of merlin-mediated contact inhibition of cell growth through interactions with CD44 in schwannoma cell lines [16]. Even though the data regarding the CD44 function on meningioma cells favor CD44 as to contribute to the invasiveness and anaplasia of meningiomas, several studies have shown that CD44 may have biphasic effect on meningioma cell behavior-that is CD44 favors increased migration in low concentration whereas it causes inhibition in meningioma cell migration in its high concentrations [17]. Nevertheless, it is evident that CD44, as a cell surface marker has interactions with small cellular membrane proteins such as ezrin, moesin, and merlin. As well known, merlin protein is encoded by NF2 gene which is a tumor suppressor gene and is inactivated in biallelic fashion in more than half of spontaneous meningiomas [18-20]. However, it is not still clear if NF2 gene inactivation has any influence on the differential expression of CD44 on meningiomas or both NF2 gene inactivation and CD44 over-expression are the components of a more generalized yet uninvestigated picture.

Discussion

CD133 appears to be a specific cancer stem cell marker for GBM cells based on the current findings in the literature. However, the exact biological role of CD133 in normal stem cell and/or glioma cell remains obscure. Furthermore, the molecular and genetic diversity of GBM cells may be explained by the existence of more than one single universal glioma stem cells with potentially different cellular markers other than CD133. Hence, any therapeutic approach targeting CD133-positive glioma cells should consider these possible obstacles.

On the other hand, the function and structural features of CD44 in meningiomas were far better identified than those of CD133 in gliomas. CD44 over-expression seems to be correlated with anaplasia and increased motility of meningioma cells. However, these findings are mostly derived from histopathological and flow cytometric studies. Thus, further studies are necessary to investigate the interactions of CD44 and merlin protein more clearly at the molecular level.

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