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The role of octamer binding transcription factors in glioblastoma multiforme☆

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ABSTRACT

A group of transcription factors (TF) that are master developmental regulators of the establishment and maintenance of pluripotency during embryogenesis play additional roles to control tissue homeostasis and regeneration in adults. Among these TFs, members of the octamer-binding transcription factor (OCT) gene family are well documented as major regulators controlling the self-renewal and pluripotency of stem cells isolated from different adult organs including the brain. In the last few years a large number of studies show the aberrant expression and dysfunction of OCT in different types of cancers including glioblastoma multiforme (GBM). GBM is the most common malignant primary brain tumor, and contains a subpopulation of undifferentiated stem cells (GSCs), with self-renewal and tumorigenic potential that contribute to tumor initiation, invasion, recurrence, and therapeutic resistance. In this review, we have summarized the current knowledge about OCT family in GBM and their crucial role in the initiation, maintenance and drug resistance properties of GSCs. This article is part of a Special Issue entitled: The Oct Transcription Factor Family, edited by Dr. Dean Tantin.

1. Introduction

TFs related to pluripotency and stemness are developmental regulators of self-renewal and cell differentiation. The dissection of transcriptional networks has provided invaluable information regarding the nature of the master regulators that control entire gene expression signatures that drive the phenotype of normal and malignant cells of the brain. Understanding how such transcriptional networks regulate transitions into physiological or pathological cellular states remains a central challenge in systems biology. Stemness is a hallmark of tumor aggressiveness in GBM, but the regulatory programs responsible for implementing the molecular signature associated with this phenotype are largely unknown [1]. Members of the *OCT* gene family (HUGO nomenclature: POU class homeoboxes and pseudogenes) are recognized as being among the master TFs controlling the expression of genes responsible for pluripotency and embryogenesis during the early stages of development. Recently, multiple studies have implicated the altered expression and function of OCT family members in the pathogenesis of several types of cancer, including GBM. In this review, we discussed current knowledge on the effects of OCT deregulation in GBM and the role of OCT in the maintenance of GSCs. Targeting of pluripotency TFs, including OCT4, represents a promising therapeutic approach that may improve overall survival and reduce tumor relapse in GBM patients [2]. OCT4 and OCT7 [3–5], together with other master regulators, SOX2, SALL2, OLIG2 and NANOG, have the most established anti-differentiation, pro-stemness and pro-tumorigenic function of all the OCT TF family members in stem cells, including GSCs. Among genes regulated by these TFs are genes encoding key signaling pathways that control pluripotency and self-renewal. At the same time, they repress genes that promote differentiation [5,6]. These TFs are also involved in an auto-regulatory loop controlling their own expression, and targeting one of these TFs may have a broad effect on pluripotency [7]. Although these studies add additional layers of complexity and underscore the importance of network-based rearrangements in the heterogeneous subpopulation of GBM cells; their global functions remain poorly understood in the context of multifaceted phenotype of this disease.

2. Glioblastoma multiforme: characteristics, subtypes and cancer stem cells

GBM is the most frequent and aggressive primary brain tumor in adults, and despite improvements in therapy and progress in understanding of GBM pathophysiology, the prognosis of GBM patients remains poor, with a median overall survival of only 14.2 months [8–10]. The treatment modalities for GBM include maximal safe surgical resection, followed by irradiation and chemotherapy with temozolomide (TMZ) [8]. GBM is an extremely aggressive, complex and heterogeneous tumor composed of distinct cellular components, including

Abbreviations: TF, transcription factors; GBM, glioblastoma multiforme; OCT, octamer binding transcription factor; TMZ, temozolomide; CSC, cancer stem cells; GSC, GBM stem cell; NSC, neuronal stem cell.

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tumor cells with different phenotypes, genotypes and epigenetic characteristics, associated astrocytes, infiltrating immune cells and microglia, abnormal vasculature and extensive necrotic and hypoxic zones (Fig. 1A).

WHO classification of gliomas into grades I–IV is based mainly on the histological features of the tumor [11], and frequently does not reflect the molecular heterogeneity of the disease. Our knowledge of GBM biology had been enriched immensely by the advent of molecular characterization and cancer genomics. Large-scale, high-throughput characterization of GBM has clearly identified a combination of genetic, epigenetic, and transcriptome modifications defining four GBM subtypes. Despite intra- and inter-tumoral heterogeneity at the molecular and histopathological levels, GBMs can be divided into four major subtypes based on distinct transcriptional signatures as well as particular genetic aberrations: the proneural, neural, classical and mesenchymal subtypes [12–14]. The classical subtype is characterized by extreme *EGFR* amplification, homozygous deletion of *CDKN2A*, and wild-type *TP53*. Unlike what is observed in classical GBM tumors, *TP53* is frequently mutated in proneural GBM (in 54% cases), and this subtype is also characterized by frequent mutations in the *IDH1* and *PDGFR-α* genes, as well as a G-CIMP^{+} (GBM-CpG island methylator) phenotype. This subgroup is most prevalent in younger patients, and these tumors demonstrate global hyper-methylation, associated with *IDH1* mutations and better survival [13,15]. The mesenchymal subtype is defined by frequent mutations in the *NF1* (in 37% cases), *PTEN* and *TP53* tumor suppressor genes, whereas no distinctive mutations have been demonstrated in the neural subtype of GBMs [16]. Apart from these several gene mutation in GBM subtypes, adjuvant therapy with TMZ undoubtedly leaves an imprint in the genome evolution in low grade glioma. TMZ-treated patients have been frequently related to have tumor recurrence with high rate of mutation in the genes associated with inactivation of the mismatch repair pathway and subsequently underwent to malignant progression to GBM [17]. Recently, single-cell RNA analysis of cells from several GBM patients revealed a mixture of cells with different subtypes in each individual patient, adding an additional level of complexity to the pathobiology of GBM [7]. The impact of such complex heterogeneity will not be fully understood without describing the self-renewal and drug resistance properties of subpopulation of GBM cells, having stem like properties.

To understand the critical role and origin of cancer stem cells (CSC) in the pathogenesis of GBM, we first must consider earlier stochastic models. These models theorized that all cells in a tumor, after clonal evolution of acquired genetic mutations, are responsible for tumor growth, and that most clones are highly proliferative and tumorigenic, with the capacity to develop tumors after transplantation. In the last two decades, however, the stochastic model has been largely supplanted by the concept of CSC, which acknowledges that cancers are heterogeneous entities with cellular hierarchies and small subpopulations of self-renewing cells capable of driving tumor initiation, growth, propagation, and resistance to therapy [18]. The CSC concept was first described in acute leukemia models, where a subset of tumor cells could self-renew and propagate leukemia in vivo after xenotransplantation into athymic mice [19,20]. Compelling evidence exists that supports the presence of CSCs in numerous solid tumors, including GBM [21].

Because of inherent characteristics of GBM, such as invasiveness that prevents total resection and resistance to radio- and chemotherapy, almost all GBMs recur after treatment. A relatively small sub-population of GSCs, is highly tumorigenic [21–23] and therapy-resistant [24]. This subpopulation has the ability, upon intracranial transplantation, to generate a tumor that recapitulates the cellular heterogeneity and molecular characteristics of the parental tumor, indicative of its crucial

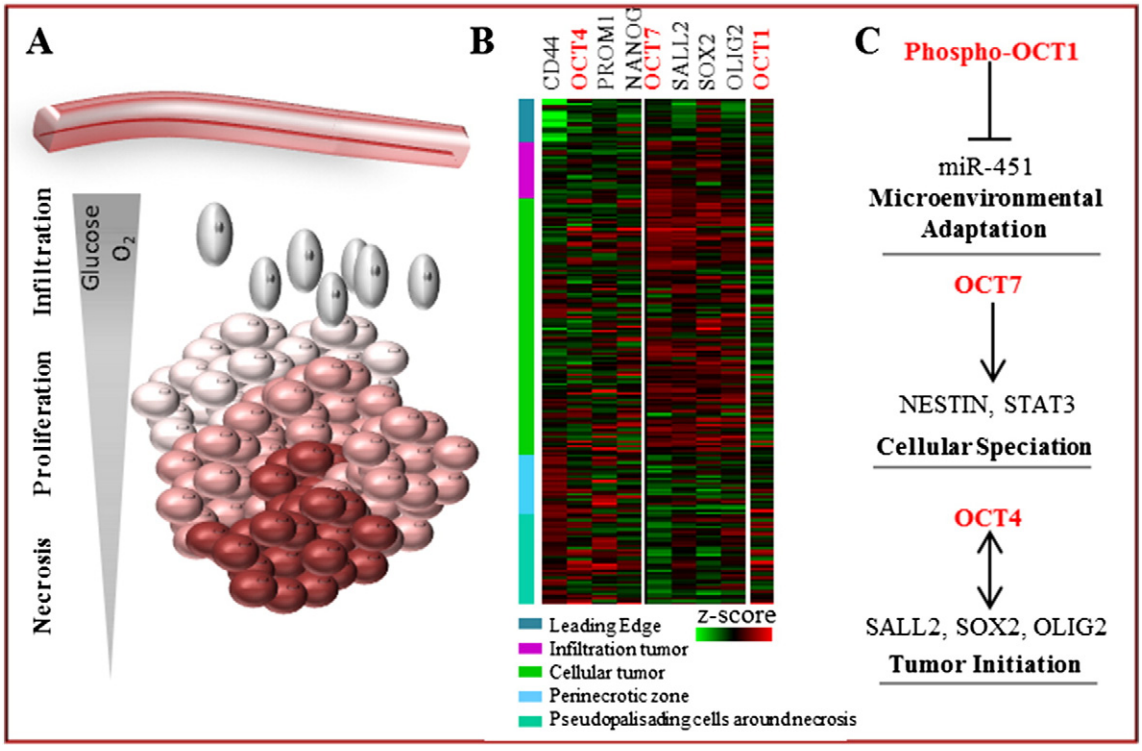

Fig. 1. Schematic representation of OCT family expression and function in GBM microenvironment. A. Cellular heterogeneity reflects the complexity of the GBM ecosystem. Subpopulations of GBM cells grow in divergent intra-tumoral anatomic sites determined by microenvironmental cues (e.g. hypoxia, nutrient availability) which may contribute to tumor cell speciation, growth and invasion. B. OCTs are differentially expressed in intra-tumoral anatomic niches. Expression of OCT4 is prevalent in hypoxic, necrotic zones, while OCT 7 is expressed almost exclusively in proliferative, cellular areas. Expression of OCT1 is not specific to any distinct, intra-tumoral anatomic site. Ivy GAP database-based expression of OCTs signature in different areas of GBM for annotated genes is shown. C. OCT TFs determine GBM cell fate. Overexpression of OCT7 and OCT4, along with their partner TFs in neural stem cells leads to cellular speciation and tumor initiation, while AMPK-dependent, phospho-OCT1-mediated de-activation of miR-451 signaling allows microenvironmental adaptation which results in decreased proliferation and increased migratory phenotype.