

## Neural stem cells and glioblastoma stem cells: Redefining concepts

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### ABSTRACT

Stem cells (SCs) represent a distinctive population of undifferentiated cells with the extraordinary ability to self-renew and differentiate into multiple cell types. Owing to this, SCs play a crucial role in maintaining tissue homeostasis, providing a source for the replacement of cell losses due to normal wear and tear. In addition, SCs display an unquestioned therapeutic potential, which has resulted in the development of several cell therapies for the treatment of different types of diseases. However, despite their remarkable potential, the therapeutic use of SCs must still face several challenges, which include ethical, legal and technical issues. Ethical and legal concerns are mainly related to the use of SCs obtained from human embryos, while technical problems mostly arise from the difficulty of appropriately directing the differentiation of the SCs to meet the tissue's needs and the occurrence of events such as immune rejections. In addition, the safety of SC-based therapies is also under debate. Although they may offer a useful and harmless treatment for many pathologies, including some incurable and/or life-threatening diseases, a potential risk of tumorigenicity may also exist in some cases. Accumulating evidence also implicates SCs as the origin of, at least, some types of cancer. This is the case of glioblastoma (GBM), the most prevalent glioma type in adults, whose origin has been related to postnatal neural stem cells (NSCs), mainly located in the subventricular zone (SVZ) and the dentate gyrus in the hippocampus. It has been proposed that these NSCs may give rise to glioblastoma stem cells (GSCs), which through complex interactions with the tumor microenvironment exert a crucial effect on tumor growth and development.

**Abbreviations:** ADSC, Amnion-derived stem cells; AML, Acute myeloid leukemia; ASC, Adult stem cells; BBB, Blood-brain barrier; CAM, CNS-associated macrophages; CIC, Cancer initiating cells; CMSC, Chorionic mesenchymal stromal cells; CSC, Cancer stem cells; CSF, Cerebrospinal fluid; CTL, Cytotoxic T lymphocytes; ECM, Extracellular matrix; EGF, Epidermal growth factor; EpiSC, Epiblastic stem cells; ESC, Embryonic stem cells; EV, Extracellular vesicles; FGF, Fibroblast growth factor; FSC, Fetal stem cells; GAM, GBM-associated macrophages; GBM, Glioblastoma; GSC, Glioblastoma stem cells; HIF, Hypoxia inducible factor; HSC, Hemopoietic stem cells; ICM, Inner cell mass; IL, Interleukin; IPSC, Induced pluripotent stem cells; LIC, Leukemia initiating cells; LSC, Leukemia stem cells; MDSC, Myeloid-derived suppressor cells; ME, Microenvironment; MES, Mesenchymal; MMP, Matrix metalloproteinase; MpSC, Multipotent stem cells; NE, Neural; NPC, Neural progenitor cells; NSC, Neural stem cells; NSCC, Non-stem cancer cells; OCM, Outer cell mass; OSC, Oligopotent stem cells; OxPhos, Oxidative phosphorylation; PDGF, Platelet derived growth factor; PN, Proneural; PNS, Peripheral nervous system; PNSC, Perinatal stem cells; PSC, Pluripotent stem cells; RSC, Resident stem cells; SC, Stem cells; SGZ, Subgranular zone; SSC, Somatic stem cells; SVZ, Subventricular zone; TAN, Tumor associated neutrophils; TCA, Tricarboxylic acid cycle; TGF, Transforming growth factor; TIC, Tumor initiating cells; TIME, Tumor immune microenvironment; TME, Tumor microenvironment; Treg, T regulatory cells; TSC, Totipotent stem cells; TiSCs, Tissue stem cells; UCSC, Umbilical cord stem cells; USC, Unipotent stem cells; VEGF, Vascular endothelial growth factor.

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## 1. Stem cells (SCs): types and functional features

The term “stem cell” was first introduced (as *Stammzelle*, in German) in 1868 by Ernst Haeckel, a prominent German physician and biologist who also postulated the renowned “biogenetic law” or Meckel-Serres law. This postulate, frequently summarized as “ontogeny recapitulates phylogeny” states that, during ontogenesis, embryos pass through successive stages that represent the adult forms of less complex organisms. In this context, Haeckel applied the term SC to both the fertilized egg, which gives rise to all cells of an organism, and the (alleged) ancestor unicellular organism from which all multicellular organisms evolved (Ramalho-Santos and Willenbring, 2007; Maehle, 2011; Richtsmeier, 2018). Although the biogenic law was discredited in the early twentieth century, the term emphasized the importance of the fertilized egg, partly of fatherly and partly of motherly origin, as the stem of all the cells of a multicellular organism. Later in that century, Theodor Heinrich Boveri and Valentin Häcker used the term “stem cell” to describe embryo cells committed to produce more specialized cells.

Modern stem cell biology emerged in the mid-twentieth century with the identification of hematopoietic stem cells (HSCs) in mouse bone marrow (Siminovitch et al., 1963), confirming earlier hypotheses that all blood cells arise from a common precursor. Nowadays, SCs are defined as undifferentiated cells that have the remarkable abilities to (1) self-renew and (2) develop into many different cell types and functional tissues. These properties largely rely on the capacity of SCs to undergo asymmetric cell division, producing two different daughter cells: a true SC that retains stemness, and a progenitor cell committed to differentiation with limited self-renewal and inability to undergo asymmetric division. This crucial capacity of SCs for undergoing asymmetric division is consequence of their intrinsic characteristics but may be also modulated by extrinsic mechanisms mainly governed by the interaction between the SCs and the SC niche microenvironment (Ramalho-Santos and Willenbring, 2007; Knoblich, 2008 Feb 22; Tang et al., 2021).

Based on their plasticity, SCs are classified into five major categories: totipotent, pluripotent, multipotent, oligopotential, or unipotent (Table 1) (Denker, 2015; Zakrzewski et al., 2019). Totipotent SCs (TSCs), and less frequently denominated omnipotent SCs, devise the highest differentiation potential, since they have the capacity to produce all cell types of the organism, and all the extra-embryonic structures. Totipotency is a characteristic of zygotes and early developing (2–4 cells stages) embryonic cells (Fig. 1).

In contrast, pluripotent SCs (PSCs) can differentiate to any cell of the organism, as well as some extraembryonic structures such as the yolk sac or the amnion, but not to trophoblast-derived structures. There are three types of PSCs: embryonic stem cells (ESCs), epiblastic SCs (EpiSCs) and induced PSCs (iPSCs). In humans, ESCs first appear around the fourth day of embryonic development, when the differentiation between the

inner cell mass (ICM) and the outer cell mass (OCM) occurs (Fig. 1). ICM cells retain the capacity of given rise to the proper embryo and are, therefore, pluripotent cells. In contrast, OCM cells, are multipotent since they can only originate extra-embryonic structures. As embryo development proceeds, the ESCs originate the two layers that comprise the bilaminar embryo: the epiblast and the hypoblast. Only EpiSCs retain the pluripotency, while hypoblast cells, are multipotent and do not contribute to create embryonic structures.

At odds with ESCs and EpiSCs, the third type of PSCs, the iPSCs, are not originated during normal embryo development. They were first generated in 2006, by Sinhya Yamanaka (Takahashi and Yamanaka, 2006) which was awarded with the Nobel prize in Physiology or Medicine in 2012 for the discovery that mature cells can be reprogrammed to become pluripotent (Denker, 2015; Takahashi and Yamanaka, 2006; Dottori et al., 2023). Therefore, iPSCs provide a suitable choice to overcome some technical and ethical problems related with the use of either ESCs or EpiSCs, both in research and as a therapeutic tool (Yamanaka, 2020). iPSCs should not be confused with trans-differentiated somatic cells, which are mature somatic cells generated through trans differentiation, a reprogramming process that allows the conversion of one terminally differentiated cell type into a different terminally differentiated cell type, but without transition through a pluripotent stage (Ng et al., 2022).

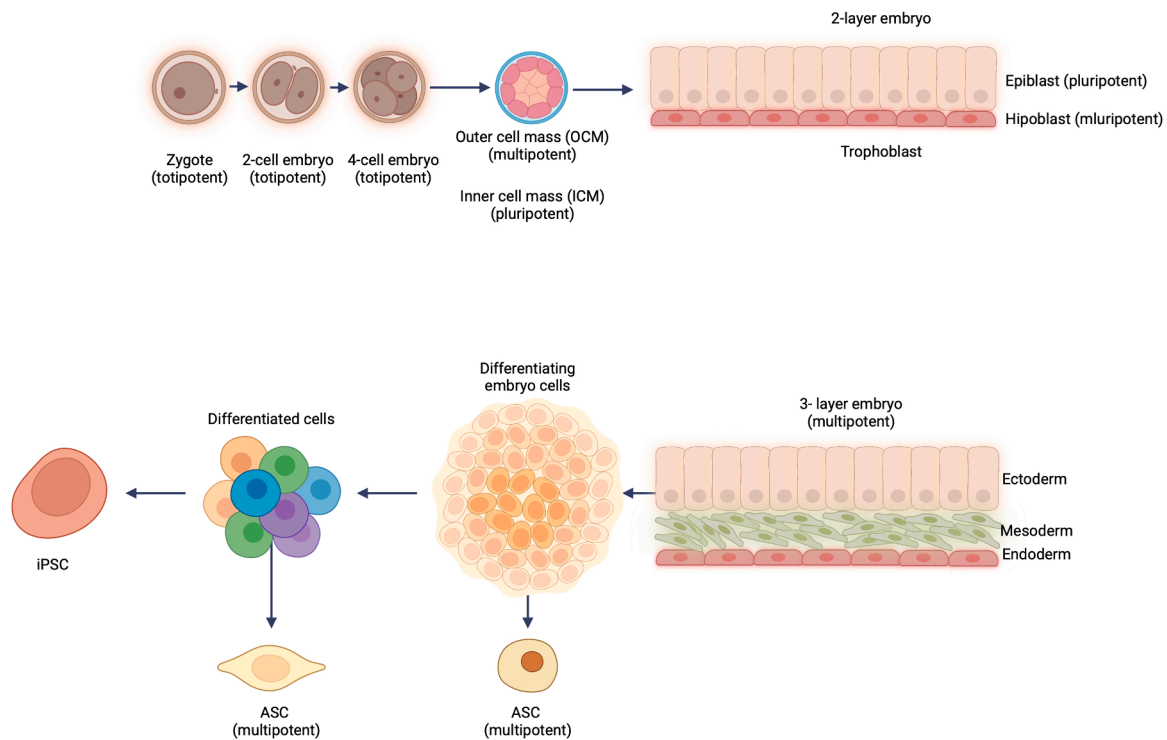
The third category of SCs, according with their plasticity, are the multipotent SCs (MpSCs), which can only differentiate into a limited number of cell types. MpSCs are present in both fetal and postnatal tissues. As previously mentioned, the first type of MpSCs that appear during embryonic development are originated from the OCM, although they do not contribute to any element of the proper embryo. Most of MpSCs SCs originated during embryonic development, proceed from the EpiSCs that form the three germ layers (ectoderm, mesoderm and endoderm) of the trilaminar embryo disc. Consequently, no pluripotent cells are present in the embryo beyond this stage and, because of this, all SCs present in the trilaminar disc and subsequent developmental stages (late embryo and fetus) are collectively termed as fetal SCs (FSCs). As the embryo development progresses, most of its cells differentiate, and only limited amounts of SCs are maintained in the different developing tissues. These SCs are also named tissue stem cells (TiSCs) and, although they are genuine MpSCs, the number of different cell types that can originate is shortened, usually restricted to the cell types of that specific tissue. Owing to this, TiSCs are, sometimes, considered as oligopotential stem cells (OSCs), in contrast with the “true” MpSCs that can give rise to any cell from their lineage.

MpSCs /OSCs can be also found in many extraembryonic tissues in late stages of development such as the amniotic membrane (usually termed as amnion-derived stem cells, ADSCs), the chorion (chorionic mesenchymal stromal cells, CMSCs) or the umbilical cord (umbilical cord stem cells, UCSCs) (Marcus and Woodbury, 2008; Paliwoda et al., 2022). In the clinical asset, these extraembryonic tissues constitute a valuable source of SCs for cell therapy, mainly because they can be harvested after birth (Ishii, 2014; Zhu et al., 2024), thus overcoming the profound ethical concerns and objections against the medical use of cadaveric fetal tissue, which is frequently derived from cases of elective abortion. Because of this, they are frequently named perinatal SCs (PNSCs), despite they are already present in the developing embryo.

Other to the embryo, MpSCs can be also found during postnatal life in most (if not all) tissues. Because they are present throughout postnatal life, these MpSCs are denominated adult stem cells (ASCs), or less frequently, somatic stem cells (SSCs), resident stem cells (RSCs), or TiSCs, although the last three denominations do distinguish between prenatal or postnatal. ASCs play a major role in the maintenance of tissue homeostasis during postnatal life. Although they are normally in a quiescent state, they can be activated to proliferate so their progenies can replace cell loss secondary to tissue wear-and-tear or injury (Zakrzewski et al., 2019; Paliwoda et al., 2022; Gurusamy et al., 2018). As most FSCs, ASCs can form a reduced number of types of differentiated

**Table 1**  
Categories of SCs.

SC type	Origin	Plasticity
Totipotent/ Omnipotent	Zygote 2–4 cell stage embryo	All cell types All extra-embryonic structures
Pluripotent	Embryo inner cell mass (Embryonic Stem Cells) Epiblast (Epiblastic Stem Cells) Modified adult cells (Induced Pluripotent Stem Cells)	All cell types
Multipotent	Fetal or adult tissues: Fetal Stem Cells Adult Stem Cells	Several cell types
Oligopotential	Fetal or adult tissues: Fetal Stem Cells Adult Stem Cells	Several cell types
Unipotent	Adult tissues	One cell type



**Fig. 1.** Classification of SCs according with their potency. For simplicity, some types of SCs are omitted. Totipotency is only present in the zygote or early embryo cells (2–4 cells stages). As embryo development progresses to compaction stage, the differentiation into inner or outer mass cells implies a loss of cellular potency. Inner cells become pluripotent, with the capacity to give rise to the proper embryo and some extraembryonic structures, while outer cells become multipotent and originate the trophoblast. At the 2-layer stage, the embryo consists of epiblast and hypoblast, both derived from the inner cells mass. However, only epiblast cells retain pluripotency, while hypoblast cells become multipotent, giving rise to the primitive endoderm and the yolk sac. At the 3-layer embryo stage, every germ layer (ectoderm, mesoderm and endoderm) contains multipotent cells that will give rise to different cell types of the developing embryo. During this process, most of the cells will be transformed into differentiated cells, although multipotent cells will be present in both fetal and postnatal tissues. Though terminal differentiation is not reversible under normal conditions, it can be induced in the laboratory, given rise to the iPSCs.

cells, and, consequently, they can be also considered OSCs instead of MpSCs.

Finally, unipotent SCs (USCs) are those SCs that can only differentiate into a single specific cell type. Germline stem cells are the best characterized USCs, but they have been also described in other tissues such as mammary gland, skeletal muscle or liver (Alonso et al., 2003; Duncan et al., 2009; Visvader and Lindeman, 2011; Cheng et al., 2022).

In the clinical, SCs have been persistently considered as a potential source for the treatment of several conditions for almost one century, that is, even before the present-day concept of SCs was established. Following the discovery of insulin by Banting and McLeod, and the potential benefits of insulin administration for the treatment of diabetes mellitus, the first human fetal pancreatic transplantation was performed in 1928 (Fichera, 1928), with subsequent attempts in the following years. Though those therapeutic approaches failed, they paved the way for the use of fetal tissues (i.e. FSCs) in therapy. Nowadays, SC-based therapy, is mainly centered on the use of MpSCs, (either fetal, adult or perinatal), though iPSCs are emerging as the new gold-standard.

To the present, the use of ESCs for cell therapy is hampered by both ethical/legal and technical limitations. The main ethical/legal issue depends on the fact that the almost only source of PSCs are the ESC isolated from fertilized eggs, left over from in vitro fertilization procedures, that must be destroyed to isolate the ESCs. Alternatively, FSCs can be obtained from cases of elective abortion, which also rises profound discussion and whose use is even banned in several countries (Jonlin et al., 2025). Because of this, PNSCs constitute a valuable source of SCs in the clinical asset, as they can be harvested after birth (Ishii, 2014; Zhu et al., 2024), thus overcoming the ethical concerns and objections against the medical use of ESCs/FSCs. Nevertheless, notwithstanding their obvious ethical advantages and their promising results in

some diseases, their true therapeutical potential must be still envisaged.

However, even if ethical/legal issues are far from being resolved, technical limitations are even more impeding. Despite ESCs could be (theoretically) used to obtain every cell type required, due to their pluripotency, purposefully differentiation of ESCs to obtain the differentiated cell type required cannot be currently accomplished. This technical limitation could be alleviated if FSCs are used, since they are multipotent and, therefore, focused differentiation is, at least in theory, easier to achieve. In this regard, promising results have been obtained in the lab when FSCs were used to treat several kinds of disorders, mainly neurological, but also hematological or immunological (Poliwoda et al., 2022; Ishii, 2014). However, because FSCs are multipotent, they cannot be used as a source for every cell type of the organism. Another technical limitation arises from the fact that using allotransplanted cells may activate an immune response from the host, either if ESCs or FSCs are used. Finally, some concerns also exist regarding the safety of ESC or FSC transplantation, mainly related with their possible transformation.

Because of those limitations, ASCs are also envisioned as a conceivable source for cell therapies, which lack most of the ethical concerns related with the use of ESCs/FSCs and, when autotransplantation is possible, also the complications related with the immunological rejection. In this regard, HSC transplantation has become a successful treatment for various hematological disorders, like some types of leukemia or bone marrow failure, and promising results have been obtained with other types of ASCs (Zakrzewski et al., 2019; Gurusamy et al., 2018; Li et al., 2022). However, using ASC has also two important drawbacks, which significantly shrinks their therapeutical potential. First, purposefully differentiation has not been achieved in some types of ASCs. Second, and because of their anatomical localization, it is, sometimes, impossible to obtain the adequate number of cells needed for therapies.

Finally, although they are usually considered to be lower than when using ESCs/FSCs, some safety concerns also exist (Nie et al., 2023; Tang et al., 2017).

Due to its capacity to overcome some of those limitations, iPSCs are emerging as the new gold standard for the use of SCs in precision medicine. iPSCs can provide a reliable source of easily accessible and expandable PSCs, while avoiding the ethical concerns associated with the use of ESCs or FSCs and overcoming the limitations of accessibility of some ASCs. However, despite their remarkable potential, the therapeutic use of SCs must still face several challenges. As with other PSCs it is necessary to refine the control of their differentiation into specific cell types, and to reduce the occurrence of untoward immune responses. In addition, the potential risk of tumorigenicity may be even higher with this type of SCs because of their great plasticity and capacity of unlimited proliferation (Zakrzewski et al., 2019; Mousaei Ghasroldasht et al., 2022).

## 2. Neural stem cells (NSCs)

NSCs are MpSCs from ectodermic lineage, which are responsible for the formation of both CNS and PNS (peripheral nervous system) during embryonic development. NSCs are the most primordial and uncommitted neural cells, with the remarkable ability of undergoing asymmetrical divisions, which allows them to both self-renew and develop into any type of differentiated neural cell type (Kriegstein and Alvarez-Buylla, 2009; Ma et al., 2009; Teng et al., 2008). In early steps of development, NSCs are located lining the wall of the neural tube and originate different types of neural progenitor cells (NPCs). NPCs have also the capacity to divide and differentiate into different types of neural cells. However, unlike NSCs, they have a limited proliferative capacity and cannot undergo asymmetric division and, therefore, cannot self-renew. For any given region of the developing nervous system, the different types of neural cells arise from NPCs in a temporally defined sequence, with neurons appearing first, followed by glial cell generation (Okano and Temple, 2009).

Other to the embryonic period, NSCs are also present in the postnatal CNS of all mammalian species investigated so far, including humans. Postnatal NSCs are not widely distributed throughout the CNS but restricted to distinct areas of the brain, spinal cord, or retina, denominated neurogenic niches (Ma et al., 2009; Bakhshinyan et al., 2021; Finkel et al., 2021; Kazanis and French-Constant 2011; Llorente et al., 2022; Sanchez-Gomar et al., 2024). These complex functional structures are composed by NSCs, NPCs and differentiating cells from the neural lineage, together several types of supporting non-neural cells like podocytes, endothelial cells (blood vessels) or microglia, as well as cytoplasmic extensions from neighboring cells and axon endings. In addition, acellular components of the extracellular matrix (ECM) also participate in making the niche. Core ECM components of the neurogenic niches include different types of collagens, elastin, laminin(s), fibronectin and proteoglycans, together with basement membrane-associated fractions, specialized ECM structures, that contribute to regulate the fate of NSCs (Kazanis and French-Constant, 2011; Valamparamban and Spéder 2023). This complex functional organization provides the physical and biochemical specifications required to maintain the pool of active NSCs required to support the regenerative capacity of the nervous system for the whole life of an individual (Finkel et al., 2021; Llorente et al., 2022; Aimone et al., 2014; Matarredona and Pastor, 2019).

In humans, the two major brain NSCs niches are the subventricular zone (SVZ) of the lateral ventricle and the subgranular zone (SGZ) of the dentate gyrus in the hippocampus (Finkel et al., 2021; Kazanis and French-Constant 2011; Llorente et al., 2022; Sánchez-Gomar et al., 2024; Matarredona and Pastor, 2019; Cebrian Silla et al., 2021; Baur et al., 2022; Liang et al., 2025). The SVZ is one of the largest regions supporting the generation of new neural cells in the adult mammalian brain. The SVZ is richly vascularized and displays a highly organized and

distinctive cytoarchitecture composed of a monolayer of ependymal cells and a dense network of progenitors, differentiating neural cells and supporting cells that surround the NSCs. SVZ NSCs, usually have a characteristic bipolar morphology, with a short process that contacts the ventricle and a long process that reaches nearby blood vessels allowing direct exposure to circulating signals. The SGZ is located at the interface between the granule cell layer and the hilus of the dentate gyrus in the hippocampus. It is also richly vascularized and displays a highly organized cytoarchitecture. SGZ NSCs show a radial glia-like morphology, characterized by a triangular soma and long radial processes that extends through the granule cell layer, providing structural scaffolding and signaling support.

Although SVZ and SGZ display differences in their structure and organization, they share several functional characteristics in terms of regulation which, broadly, depends on two types of signals in both cases: intrinsic and extrinsic. Intrinsic signals are generated by the components of the neurogenic niche, which include a wealth of mediators released by the different types of neural cells, supporting cells and immune cells. All of them produce paracrine factors and exosomes that regulate the outcome NSCs, but also produce many components of the ECM, which, in turn, will also regulate NSCs destiny through cell-ECM interactions. In addition, both NSCs and NPCs communicate between them and with many of the other cells of the neurogenic niche via cell surface molecules that trigger the activation of signaling pathways that contribute to the regulation neurogenic niche. On the other side, extrinsic regulation mainly depends on diffusible signals that reach the neurogenic niche from the blood or, especially in the SVZ, from the cerebrospinal fluid (CSF), but it also includes the innervation of the neurogenic niches by neurons located in distant brain regions. Extrinsic signals contribute to maintain the optimal conditions of the niche microenvironment (ME) and are, probably, one of the main factors coordinating the activity of the neurogenic niches with the physiological needs of cellular replacement (Finkel et al., 2021; Kazanis and French-Constant, 2011; Matarredona and Pastor, 2019; Arce et al., 2013). Adding evidence suggests that NSCs may be responsible of the production of new neural cells under the influence by various physiological, pathological, and pharmacological stimuli (Kriegstein and Alvarez-Buylla 2009; Finkel et al., 2021; Arce et al., 2013; Morrison and Kimble, 2006), thus playing a major role in maintaining tissue homeostasis by replacing neural cells lost because of tissue wear and tear, or owing to injuries or diseases (Devesa et al., 2014; Gage and Temple, 2013; Magavi et al., 2000). In this regard, maintaining the structural and functional characteristics of the niche ME is essential for NSCs function, and accumulating evidence demonstrates the existence of a direct relationship between changes in the NSC ecosystem and disease (Finkel et al., 2021; Matarredona and Pastor, 2019; Gage and Temple, 2013; Magavi et al., 2000). Furthermore, as we will profoundly discuss below, changes in the microenvironment may even prompt the transformation of NSCs and promote and maintain the development of brain tumors during early steps (Matarredona and Pastor, 2019; Loras et al., 2023).

As occurs with other types of SCs, NSCs have been proposed for the treatment of neurological disorders associated with irreversible cellular damage, such as some degenerative diseases or ischemia stroke (Nie et al., 2023; Tang et al., 2017). Unfortunately, most (if not all) of the caveats associated with the therapeutic use of SCs are present in NSCs (Zakrzewski et al., 2019; Nie et al., 2023; Tang et al., 2017; Mousaei Ghasroldasht et al., 2022; Matarredona and Pastor, 2019; Ottoboni et al., 2020). First, and despite some promising advances in disentangling NSC plasticity, purposefully differentiation of NSCs into the required neural cell type cannot be accomplished up to now, which significantly shrinks their therapeutic potential. In addition, and because of their anatomical localization, it is not possible to obtain the high number of cells needed for adequate therapies from living individuals, which makes not possible the use NSCs for auto-transplantation. The alternative strategy of using pluripotent ESCs which are, at least theoretically, an unlimited source of NSCs is

hampered by the technical and ethical limitations already mentioned above. In fact, besides the ethical considerations, directing the differentiation of ESCs to tailor the needs of a repairing neural tissue is even more challenging than when using adult NSCs and neoplastic transformation remains as a major concern when ESCs are to be used for transplantation. Similar impediments are present when using NSCs from aborted human fetuses, which also display a limited and unpredictable availability, and raise even more ethical concerns. Finally, alike ESCs, iPSCs constitute an unlimited source of NSCs, with two major advantages: the possibility of autologous transplantation, and the lack of ethical issues. However, they share the technical limitations of achieving a purposeful differentiation and a higher potential of tumorigenicity if intracerebrally transplanted. Interestingly, the risk of tumorigenesis can be decreased by differentiating the iPSC to NPC in vitro, before transplantation, and promising results have been obtained in mice, using this technical approach (Ottoboni et al., 2020).

### 3. Cancer stem cells (CSCs)

Despite the mechanisms that regulate the origin and progression of cancer are not yet completely understood, it is presently clear that malignant tumors are made up of a mixture of different types of cells, though only some of them actively proliferate (Reya et al., 2001; Rich, 2016; Wang et al., 2014). Two main theories have been developed to explain the complex mechanisms governing tumor growth: the stochastic or clonal evolution model and the hierarchy or CSC theory model. Although these models have several controversial aspects, it is important to understand that they are not completely exclusive, and some of their features may be combined in the so-called plasticity model (Rich, 2016).

The stochastic model of tumor growth proposes that all tumoral cells are genetically similar at the beginning and accumulate mutations during tumor development which drive tumor progression and increase tumor heterogeneity. Cells presenting the most aggressive phenotypes will be selected over the time, increasing tumor invasiveness and resistance to therapy. On the other hand, the CSC model, first proposed by Bonnet and Dick in (1997), establishes that most, if not all, cancer cells are originated from rare CSCs. Named in resemblance of normal SCs, CSCs are usually defined as the subpopulation of cancer cells that show some stemness features, including the ability of self-renewal and the capacity of differentiate into several (tumoral) cell types. According to this model, only the CSCs would proliferate and differentiate, giving rise to all the heterogenous cellular phenotypes found in the tumor. Therefore, although CSCs are only a small subset of the tumor cells, they would play a major role in maintaining tumor stemness, and they would be one of the key responsible for the great cellular heterogeneity found in most types of tumors. Owing to this, CSCs would be the main contributors for cancer progression, relapse and resistance to therapy. Because of these characteristics, CSCs are also denominated tumor initiating cells (TICs) or cancer initiating cells (CICs), while the remain of the tumor cells, sometimes designated as non-stem cancer cells (NSCCs), constitute the bulk of the tumor, but would not contribute to the tumor growth. During tumor progression, CSCs constantly give rise to NSCCs, with different levels of differentiation, thus generating a cellular hierarchy. In addition, NSCCs may regain stem-like characteristics due to intrinsic genetic instability or epigenetic alterations (Lu et al., 2020; Toh et al., 2017) thus contributing to tumor maintenance. This dynamic transition between CSCs and NSCCs supports the plasticity model in which the ability of cancer cells to escape terminal differentiation is the main hallmark. In some cases, stochastic transformation of some NSCCs into CSCs is even mandatory to maintain the necessary number of CSCs required for tumor growth (Rich, 2016; Wang et al., 2014; Boylan et al., 2023).

The first demonstration about the existence of CSCs was obtained at the end of the last century, in acute myeloid leukemia (AML) patients (Bonnet et al., 1997; Lapidot et al., 1994). These patients display a small

fraction of circulating leukemic cells which some hierarchic characteristics that resemble normal HSCs. Indeed, these cells can initiate a new leukemia when transferred to mice, so they were labeled as leukemia stem cells (LSCs) or leukemia initiating cells (LICs). As usually happens with other types of CSCs, LICs show enhanced resistance to therapy and are directly involved in AML recurrence. However, and despite CSCs have attracted increasing interest in the last several years, the concept of CSC is not a new one. Already in the second half of the 19th century, Cohnheim postulated that the origin of cancer was related to the uncontrolled growth of remnants of ESCs (Rich, 2016). According with Cohnheim's theory tumors were, 'atypical neoplasms of tissue based on an embryonic rudiment'. Though this theory did not initially entice broad attention, it is presently widely accepted that transformation of tissue resident SCs is one of the mechanisms that can drive tumor initiation in both solid and haemopoietic malignancies. It must be recalled, however, that this concept of CSCs is not the same as the one previously discussed, since it claims the transformation of resident SCs as the origin of cancer. Therefore, two origins may account for CSCs: transformation of tissue-resident SCs or transformation of differentiated cells that de-differentiate and acquire stem cell characteristics (Hanahan and Weinberg, 2011; Walcher et al., 2020). Given that resident SCs are multipotent and display enhanced proliferating capacity, it is believed that the transformation process requires less oncogenic events, probably involving different pathways of tumor etiopathogeneses. In any case, even when CSCs are initially originated from resident SCs, this does not rule out the possibility that NSCCs still may de-differentiate into CSCs. In fact, the existence of two different populations of CSCs has been demonstrated in different types of tumors, although their specific origin is still matter of debate.

### 4. Glioblastoma stem cells (GSCs) and the origin of glioblastoma (GBM)

GBM is the more prevalent glioma type in adults, accounting for more than 60 % of all adult brain tumors. It is also the most malignant brain tumor and ranks among the most lethal of all human cancers. GBM usually occurs as a primary tumor (about 80 % of the cases) but it can also appear as a secondary tumor, originated from the transformation of a lower grade glioma. In both cases, the tumor is characterized by fast growth, strong invasive behavior, elevated therapeutic resistance, and relapse after treatment. Unfortunately, and despite the constant progress in the understanding of the molecular mechanisms involved in GBM tumorigenesis, it continues to be a poorly understood tumor with a dreadful prognosis. At present, median overall survival is 12–16 months after diagnosis, with one of the lowest 5-year relative survival rates (4–5 %) among all cancer types (Louis et al., 2021; Ostrom et al., 2022; Tykocki and Eltayeb, 2018). Despite the application of combined therapies that may include surgical resection, radiation therapy, chemotherapy, targeted therapy, immunotherapy or electric fields, improvements on GBM survival have been moderate over the last 30 years (Khaddour et al., 2020; Khan et al., 2021; Stupp et al., 2005).

One of the most relevant characteristics of GBM is its high degree of cellular heterogeneity, that was early documented in the clinical and led GBM to be the first type of cancer to be fully sequenced (McLendon et al., 2008). Based on its molecular signature, GBM has been classified into 3 subtypes: proneural (PN), mesenchymal (MES) and classical (CL) (Phillips et al., 2006; Wang et al., 2017a), excluding the neural (NE) type considered by Verhaak et al. (Verhaak et al., 2010). These molecular typing scheme has been recently validated and is considered to have a great potential in guiding GBM diagnosis and therapy in clinical practice (Xu et al., 2024). Despite further research is still required, the three subtypes of GBM show significant differences in their biological behavior, with the MES type strongly associated with poorer prognosis, as well as some differences in the therapeutic response, within the dismal range of GBM. In fact, no attempt to refine GBM subtypes based on their molecular characteristics has been translated into better clinical

outcomes (Xu et al., 2024; Azam et al., 2020). Moreover, the huge cellular plasticity of GBM frequently increases inter- and intra-tumor heterogeneity after tumor treatment, and recurrent tumors frequently show phenotypic differences, further challenging the achievement of effective treatments (Louis et al., 2021; Tykocki and Eltayeb, 2018; Khan et al., 2021; Azam et al., 2020).

As occurs in many malignant tumors, cellular heterogeneity in GBMs is due, at least in part, to the existence of a unique population of CSCs, which are known as GSCs (Tang et al., 2021; Matarredona and Pastor, 2019; Gimple et al., 2019). Today, this distinctive cellular subpopulation is considered to strongly contribute to the core aggressive features of GBM such as angiogenesis or invasion, and to be the main reason of tumor recurrence and therapeutic resistance. Although the definition of GSC is still under debate, a conceivable description of their major characteristics has been recently provided (Gimple et al., 2019). These characteristics include the capacity to (1) self-renew, (2) initiate tumors upon serial transplantation, and (3) recapitulate tumor cell heterogeneity. All these features, which are shared with CSC from other types of tumors, have been demonstrated in cellular populations obtained from both human and rodent GBM (Almengló et al., 2020; Almengló et al., 2021; Lee et al., 2018; Liebelt et al., 2016; Singh et al., 2003; Singh et al., 2004; Xie et al., 2015; Suvà et al., 2014). However, there is also a huge heterogeneity among GSCs which has generated some controversy regarding their hallmarks, and even the term GSC is frequently used to refer to completely different populations of cells (Yang et al., 2022; Yuan et al., 2004). Moreover, the lack of universal GSC biomarkers makes it difficult to identify the GSCs and to isolate them from the NSCs present in the tumor bulk, further hampering their characterization. In this regard, while several markers have been proposed to recognize GSCs, their accuracy is still a matter of debate, with numerous studies failing to confirm their specificity and reliability. Therefore, though the search of molecular markers is a cornerstone of GBM research, it is increasingly recognized as a problematic approach, and novel methodological approaches focusing on functional signatures are emerging as an alternative to single-marker analysis. This includes the use of single-cell RNA sequencing (scRNA-seq) to identify gene signatures that define GSC behavior, or the identification of specific ribosomal markers that distinguish GSCs from the bulk tumor cells (Silver et al., 2022; Benelli et al., 2026; Johnson et al., 2022; Kim et al., 2024; Li et al., 2025; Mi et al., 2021; Yong et al., 2015).

The first biochemical marker for GSCs identified, and still the best validated biomarker available is CD133, also known as prominin-1 or AC133 (Glumac and LeBeau, 2018). CD133 is a membrane glycoprotein, encoded by the PROM-1 gene, whose physiological function remains unknown, although a prominent role in tumor progression has been demonstrated in GBM, as well as in other several cancers (Han et al., 2016). However, despite it is frequently considered as a universal marker of GSC enrichment, there are still some debates regarding its reliability as a constituent marker of GSCs, since the presence of CD133 negative GSCs has been also reported (Tang et al., 2021).

The second putative GSCs marker is CD44, a cell-surface glycoprotein involved in cell adhesion, that is regarded as the most common CSC marker in many tumor types (Thapa and Wilson, 2016; Inoue et al., 2023). CD44 expression is correlated with GBM malignance, and CD44-enriched GSCs exhibit significantly higher self-renewal capacity (Wang et al., 2017). However preferential expression of CD44 in GSCs is still under debate and an alternative role, as invasion and migration marker of GBM cells has been proposed (Jin et al., 2013).

The intermediate filament protein nestin, an extensively studied marker of NSCs, is also significantly expressed in several types of human malignancies, including higher grade GBM, and is likewise considered as a putative biomarker for GSCs (Neradil and Veselska, 2015; Lv et al., 2017). Although a definitive depiction of nestin in GSCs remains elusive, several reports have showed that it promotes GSCs proliferation, and higher nestin expression is associated with higher grade GBM (Zhang et al., 2008; Capela and Temple, 2002; Capela and Temple, 2006).

Interestingly, co-expression of nestin with other stem cell markers, specifically CD133, may significantly influence the GSCs phenotype and help to improve the clinical prognostic accuracy (Capela and Temple, 2002; Capela and Temple, 2006).

A less frequently used GSC biomarker is CD15 or SSEA-1 (stage-specific embryonic antigen 1), a renowned NSCs/NPCs marker (Capela and Temple, 2002; Capela and Temple, 2006; Kenney-Herbert et al., 2015), that was early proposed to be a GSCs marker. However, it is presently unclear the existence of a distinctive population for CD15+ GSCs (Son et al., 2009; Shen et al., 2024).

Finally, other putative GSC biomarkers include the pluripotency factors nanog, OCT-4 (octamer-binding protein transcription factor 4), and SOX-2 (sex-determining region Y-box 2), together with enzymes like aldehyde dehydrogenase 1A3 (ALDH1A3) or glycerol-3-phosphate dehydrogenase 1 (GPD1) and a wealth of other proteins that include cytoskeleton components (PDLIM1, also known as CLP36); a member of the tumor necrosis factor (TNF) receptor family (CD70, also known as CD27L), calcium-binding proteins (S100A4); membrane receptors (leucine-rich repeat-containing G protein-coupled receptor 5, LGR5); integrins ( $\alpha 6$  integrin) or chaperones (B23, also known as nucleophosmin or NPM1) (Stupp et al., 2005; Kim et al., 2021). Nevertheless, in most cases, both their role in tumor progression and their specific allocation to GSCs remain to be clearly established.

More up-to-date techniques, like scRNA-seq have provide significant information about the mechanisms governing tumor heterogeneity through the identification of gene regulatory networks that drive the most primitive stem cell states and may provide accurate biomarkers for patient stratification (Johnson et al., 2022; Kim et al., 2024). Similarly, ribosomal proteins are also gaining prominence as GSCs markers, because they represent the translational reprogramming that GSCs undergo to survive. Ribosomal proteins such as RPS6 or RPL34 are significantly higher in GSCs compared to differentiated tumor cells, and overexpression of RPS6 induces stem-cell-like properties. Other ribosomal proteins like RPS11 and RPS20 are specifically upregulated in GSC clones that have survived radio or chemotherapy, and their occurrence is a more accurate predictor of tumor prognosis than traditional markers like CD133 (Silver et al., 2022; Li et al., 2025; Yong et al., 2015).

The existence of GSCs does not make, however, any claim about their role in the generation of the tumor and, as occurs with most types of cancer, it is still unclear which cells are more relevant as the source of GBM (Almengló et al., 2021; Lee et al., 2018; Alcántara Llaguno et al., 2009). In any case, and despite this longstanding debate is far from being closed, compelling evidence reveals NSCs (and/or NPCs) as the major candidates for the origin for GBM. In this regard, it has been shown that genetic manipulation of GBM-relevant pathways in adult NSCs/NPCs can give rise to malignant astrocytomas, whereas this outcome is not observed in more mature cell types (Zhu et al., 2005a; Zhu et al., 2005b; Tomasetti et al., 2017). The hypothesis of NSC as the origin of GBM is also in keeping with the fact that multiple oncogenic mutations are necessary for GBM tumorigenesis, and most of them are attributable to DNA replicative damage. Therefore, since NSCs possess unlimited growth potential, it seems conceivable to speculate that they are the CNS cell type that, more easily, can accumulate enough divisions to allow the buildup of the series of *de novo* somatic mutations that are required to allow their uncontrolled, niche-independent, proliferation (Walcher et al., 2020; Li et al., 2015). In this regard, it has been shown that long-term culture of mouse embryonic NSC induces their transformation into cells that are able to form GBMs when orthotopically inoculated in adult mice (Almengló et al., 2021; Lee et al., 2018). This finding demonstrates that the accumulation of divisions in NSCs may be the only drive needed for oncogenic transformation to occur.

As we mentioned before, postnatal NSC are restricted to specific neurogenic niches, among which, the SVZ may be of special relevance in the genesis of GBM (Matarredona and Pastor, 2019; Lee et al., 2018). The SVZ lines the lateral ventricles of the brain and, although neurogenesis in this area may endure throughout life, SVZ-NSC mainly give

rise to glial cells (Matarredona and Pastor, 2019; Loras et al., 2023). In addition, SVZ-NSCs share many common features with GSCs, and are more susceptible to oncogenic transformation than SGZ-NSCs (Mughal et al., 2018; Sanai et al., 2005; Seoane et al., 2008). Furthermore, it has been recently obtained molecular genetic evidence from both patient brain tissue and genome-edited mouse models indicating the accumulation of low-level GBM driver mutations in normal SVZ tissue, which equivalent to those observed, at high levels, in their matching tumors (Lee et al., 2018). Indeed, SVZ-NSCs carrying those driver mutations have been found to migrate from the SVZ and lead to the development of high-grade malignant gliomas in distant brain regions in both humans and mice (Lee et al., 2018). Therefore, it can be envisaged that NSCs located at the SVZ could be considered as the main source of GBM (Lee et al., 2018; Lv et al., 2017), although the existence of other cells of origin of GBM cannot be ruled out. In this respect, there is evidence indicating that GBM may also arise from the transformation of differentiated astrocytes after reprogramming (Seoane et al., 2011; Friedmann-Morvinski et al., 2012; Friedmann-Morvinski and Verma, 2014; Iglesias et al., 2020; Iglesias et al., 2023; Guardia et al., 2020). In any case, it must be taken in consideration that, in most of those studies, the genetic manipulation that led to GBM transformation was induced in GFAP-expressing cells. Therefore, the involvement of astrocyte precursors or even GFAP-expressing NSCs cannot be completely discarded. In this regard, it is interesting to point that two subtypes of GSCs have been identified (Lottaz et al., 2010; Mao et al., 2013; Nakano et al., 2015; Richards et al., 2021), based on their gene expression profiles and distinct biological characteristics: proneural (PN)-GSCs or mesenchymal (MES)-GSCs. Both types of cells were named after their association with PN and MES GBM subtypes, respectively, although their association with common tumor cell subtypes remains to be demonstrated (Garnier et al., 2019). MES-GSCs show higher rates of proliferation both in vitro and vivo and are more angiogenic invasive and resistant to radiation than PN-GSCs (Nakano et al., 2015; Birnbaum et al., 2011; Zong et al., 2015), thus resembling the phenotypes of the different CSCs populations identified in other tumors.

Given their importance in GBM initiation and/or relapse, targeting GSC has been envisaged as one of the most promising therapeutical

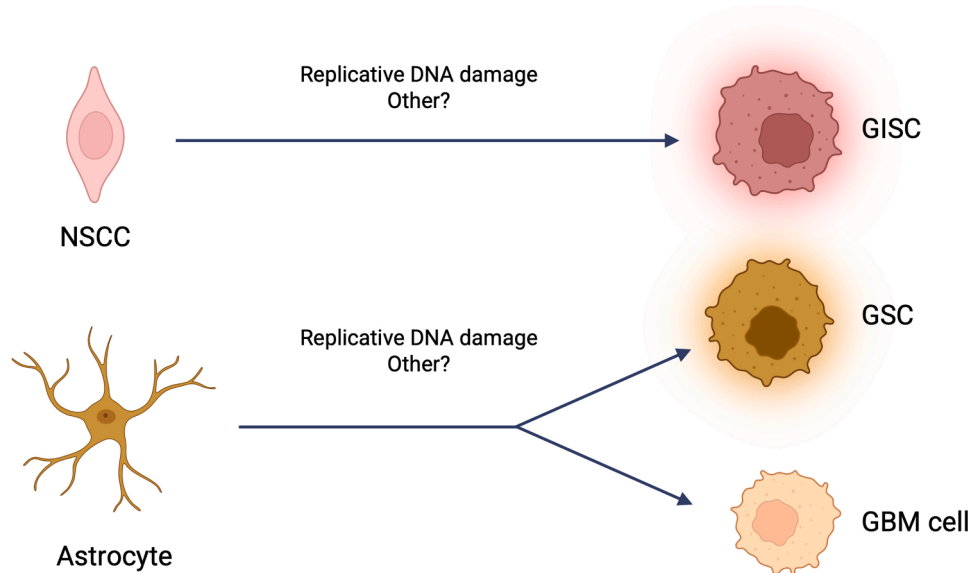
approaches (Tang et al., 2021). Unfortunately, some of the characteristics of GSC that improve their biological aggressiveness also augment their resistance to conventional treatments (Zong et al., 2015). Those mainly include (1) the presence of a highly dysregulated transcriptional landscape that circumvents the definition of specific targets for anti-cancer drugs and (2) the occurrence of epigenetic modifications that increase their biological aggressivity (Suvà et al., 2014; Biserova et al., 2021; Liu et al., 2006). In addition, GSCs usually show a low proliferative rate, mimicking normal SC behavior, and protecting them from therapies targeting dividing cells, though alternative models have suggested that GSCs may be more proliferative than the quiescent populations they are derived from (Gimple et al., 2019; Hiramatsu et al., 2017; Huang et al., 2021) (Fig. 2).

## 5. GSCs and tumor microenvironment (TME)

Once considered a silent bystander of tumorigenesis, the TME is presently recognized as one of the major elements that actively promotes tumor progression. Therefore, understanding the mechanistic insights of cancer growth not only includes the study of the tumor cells, but also the deciphering of the multifaceted interplay between them and the TME.

The TME is a complex and continuously evolving ecosystem that consists of both cellular and non-cellular constituents. In GBM, the cellular component of the TME is made up of neural cells (neurons, astrocytes, and oligodendrocytes), and different types of stromal cells, such as endothelial cells, perivascular stromal cells or glioma-associated stromal cells, together with immune cells, which include both the resident microglia and several varieties of tumor-infiltrating immune cells (Silver et al., 2022; DeCordova et al., 2020; Lootens et al., 2024). On the other side, the non-cellular component of the TME mainly consists of an altered ECM, which provides the physical scaffold for tumor growth, but also contains different signaling molecules, released by both tumoral and non-tumoral cells, that favor tumor development (Anderson et al., 2020; de Visser et al., 2023).

While the actual role of TME in GBM origin and progression is far from understood, compelling evidence indicates that it has the ability of continuously adapt to the requirements of each phase of tumor



**Fig. 2.** Proposed model for the cell origin of GBM. For simplicity, only the hierarchic theory of tumor growth is considered. (1) Compelling evidence indicates that NSCs may be the major origin of GBM. Accumulation of mutations during long-lasting replicative DNA damage and/or other types of oncogenic stress would lead to the transformation of normal NSCs into GISCs. (2) Alternatively, the possibility exists that differentiated astrocytes may undergo reprogramming induced but not completely known triggers, leading to their transformation in GSCs. Although it is unclear whether GISCs and GSC are functionally identical, both are responsible for the generation of all the spectrum of tumor cells, including the differentiated NSCCs. Stochastic transformation of terminally differentiated NSCCs into GSCs/GISCs usually occurs during tumor development.

development. This dynamic nature of TME provides the appropriate conditions to promote tumor growth and invasion, and a more active ECM remodeling is usually associated with a poorer prognosis. Furthermore, since the hallmark GBM-associated genes do not significantly change over time (Bikfalvi et al., 2023; Sharma et al., 2023; Torrisi et al., 2022), in many cases, active TME reprogramming is, together with epigenetic modifications, the main mechanism governing GBM evolution (Sharma et al., 2023; Hoogstrate et al., 2023). In this regard, it is noteworthy to signify that changes in the microenvironment may also prompt the transformation of NSC and promote and maintain the tumor development during early steps (Matarredona et al., 2019; Loras et al., 2023). Interestingly, many TME adaptations are driven by GBM cells, thus establishing a complex interplay that is essential to regulate the progression of the disease.

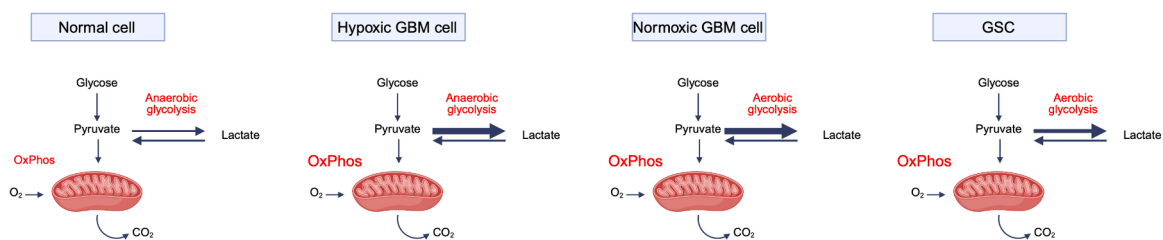
Multiple mechanisms are involved in this crosstalk between GBM and TME, which include both local regulation and distal hormonal signals and inflammatory mediators (Bikfalvi et al., 2023; Sharma et al., 2023; Hoogstrate et al., 2023). Local regulatory mechanisms mostly rely on the secretion of various types of signaling molecules and extracellular vesicles (EVs) by both tumoral and non-tumoral cells. In addition, a significant number of cell-to-cell interactions may occur at the GBM-TME boundaries, which promote TME reprogramming to favor GBM development. This includes the establishment of synaptic connections between GBM cells and neighboring CNS cells, the so-called neuro-glioma interfaces, that enable the functional integration of glioma into the brain network, facilitating neurotransmitter-based interactions that contribute to the orchestration of a TME that promotes tumor cell survival and growth (Sharma et al., 2023; Hua et al., 2022).

Although there is a wide repertoire of TME-induced modifications in GBM, most of them are mainly concentrated in the metabolic and the immune milieu. To support its aggressive growth, GBM cells must undergo a metabolic rewiring to alternative pathways, adapted to meet the increased demands of rapid growth in, usually, exhausted oxygen and/or nutrients conditions (see Sharma et al. 2023; Agnihotri et al., 2016; Cortes Ballen et al., 2024; Vijayanathan and Ho 2025). Under normal conditions, glucose serves all crucial functions of the brain which uses, approximately, 60 % of body's daily glucose intake. In the cytosol of normal brain cells, glucose is converted into pyruvate, which is then transformed in acetyl-CoA to proceed through the tricarboxylic acid cycle (TCA). As a result of this process, significant amounts of reduced coenzymes are generated, which are necessary for efficient production of ATP through oxidative phosphorylation (OxPhos). However, in GBM cells (as in many tumoral cells), most of the glucose consumed is fermented to lactate, rather than oxidized in the mitochondria (Fig. 3). Cytosolic metabolization of pyruvate into lactate (anaerobic glycolysis or glucose fermentation) is a common adaptative mechanism in response to oxygen limitation and is used by GBM cells at the hypoxic core of the tumor. However, a distinct characteristic of GBM cells is that they prefer anaerobic glycolysis for energy production, even under normoxic conditions. This metabolic hijacking, denominated aerobic glycolysis or Warburg effect, was initially described in the 1920s (Warburg et al., 1927) and, although ATP production is less efficient

when compared with OxPhos, it significantly contributes to GBM growth (Agnihotri et al., 2016; Duraj et al., 2021). Nevertheless, and despite intensive research, it is still unclear how this metabolic adaptation in GBM cells may benefit tumor development. One intriguing possibility is that some of the metabolic intermediates generated during pyruvate fermentation could be used for anabolic reactions. However, this theory is not supported by the fact that amino acids are the main bulk of anabolism in proliferating cells (Hosios et al., 2016). Alternatively, pyruvate fermentation may provide a supplementary pathway for the productions of reduced coenzymes, in situations in which high  $\text{NAD}^+$  demand surpasses ATP requirements (Luengo et al., 2021). In addition, it has been shown that lactate may increase vascular endothelial growth factor (VEGF)-induced angiogenesis, via stabilization of hypoxia inducible factor-1 $\alpha$  (HIF-1 $\alpha$ ), through a mechanism independent of hypoxia (Lu et al., 2002). Finally, increased lactate generation reduces the pH of the microenvironment, that, together with hypoxia and metabolic stress, may act as stemness-inducing stimuli, promoting the stochastic transformation of non-stem GBM cells into GSCs (Bao et al., 2006; Chen et al., 2022; Folkins et al., 2009; Heddleston et al., 2009; Li and Lathera 2012; Prager et al., 2019).

As occurs with the remain of GBM cells, the metabolic plasticity is also an important feature of GSCs, which allows them to conveniently shift among different metabolic pathways to adapt to and/or compensate for any unfavorable TME. Interestingly, although GSCs may favor either aerobic glycolysis or OxPhos as source of energy, according to environmental conditions, they usually rely more on OxPhos than other GBM cells. Also in this case, the underlying mechanisms are still unknown, but several cellular adaptations that may support the metabolic refurbishing have been described. They include (1) reduced glucose uptake and lactate production (Vlashi et al., 2011), (2) a prominent activity pyruvate carboxylase, that increases the carboxylation of pyruvate to oxaloacetate (Renoult et al., 2024), (3) increased activation of the malate-aspartate shuttle, which favors the transport of reducing equivalents across the mitochondrial membrane (Lv et al., 2024), and (4) increased activity of the V-ATPase, a proton pump that is one of the main regulators of intra/extra-cellular acidification (Storaci et al., 2025).

The second important hallmark of TME is the presence of a distinctive, highly immunosuppressive, tumor immune microenvironment (TIME) that reinforces the already immune-privileged brain milieu. The GBM TIME is characterized by abundant infiltrating immunosuppressive cells, together with the absence of cytotoxic T lymphocytes (CTLs) (DeCordova et al., 2020; Alban et al., 2020; Humphries et al., 2010; Roesch et al., 2018; Veglia et al., 2021; Vinnakota et al., 2013). This TIME not only hinders the anti-tumoral immune response of the host but also threatens the efficacy of currently available immunotherapies and, in fact, GBMs are resistant to these novel treatments, that have revolutionized the therapy of other solid malignancies primarily due to the suppression of CTL activity (Johnson et al., 2022; Lim et al., 2018). The infiltrated immune cells within the TIME mainly include T regulatory cells (Treg), myeloid-derived suppressor cells (MDSCs), tumor associated neutrophils (TANs) and GBM-associated macrophages (GAMs),



**Fig. 3.** Metabolic adaptations in GBM NSCCs and GSCs. As many cancer cells, NSCCs located in the hypoxic core of the GBM favor the obtention of ATP through anaerobic glycolysis over OxPhos. However, a distinct feature of GBM NSCCs is that they also show preference for lactate metabolism under normoxic conditions (aerobic glycolysis). In contrast, although GSCs can use both types of metabolic rewiring, they usually prefer OxPhos to obtain ATP.

which also include resident microglia (Silver et al., 2022; DeCordova et al., 2020; Alban et al., 2020; Humphries et al., 2010; Roesch et al., 2018; Veglia et al., 2021; Vinnakota et al., 2013). Among them, GAMs are the predominant immune population, comprising up to one-third of the tumor mass (Roesch et al., 2018; Vinnakota et al., 2013). Under normal conditions, tissue-resident macrophages represent the primary innate immune cells in the CNS, and constitute around 7% of non-neural cells within the CNS. GAMs come in two cellular flavors, the parenchymal microglia and the non-parenchymal CNS-associated macrophages (CAM), also known as border-associated macrophages due to their localization at the perivascular spaces, the meninges, and the choroid plexus. Microglial cells are originated from hematopoietic precursors in the yolk sac that migrate to the CNS during early embryonic development, before the blood-brain barrier (BBB) is sealed. This unique characteristic among tissue-resident macrophages allows the presence of a population of immune cells in the immune-privileged CNS parenchyma. In contrast, CAMs arise from HSCs in the bone marrow after the BBB is established, which explains their location outside the brain parenchyma, though they can also infiltrate it under some pathological conditions, which include GBM. In any case, and despite their different origin, both types of cells perform similar immune functions, and it is even difficult to differentiate between them, since no specific lineage markers have been identified to date. Because of this, both microglia and CAMs are often collectively referred as GAMs. Interestingly, a large number of signaling factors produced by GBM cells promote GAM recruitment and polarization to the M2 phenotype which, in turn, fosters tumor development through different mechanisms that include the release of: (1) growth factors such as epidermal growth factor (EGF), platelet derived growth factor (PDGF), fibroblast growth factor-2 (FGF-2), transforming growth factor beta (TGF- $\beta$ ) or interleukin (IL)-6, that directly activate the proliferation and invasiveness of GBM cells (2) proangiogenic molecules like VEGF or CXCL2 that activate angiogenesis and (3), matrix metalloproteases like matrix metalloproteinase-2 (MMP-2) and MMP-9, which favor the remodeling of the ECM. In addition, M2 GAMs release different type II immune factors such as TGF- $\beta$ , IL-4, or IL-10 that inhibit tumor-killing immune response, mainly by suppressing CTL activity (Roesch et al., 2018; Lin et al., 2023; Xuan et al., 2021).

In addition, an increasing body of evidence indicates that the critical effect TIME on GBM progression also depends on its contribution to maintain the aggressive phenotype of GSCs. Besides providing a GSC-friendly immunosuppressive milieu, most of the paracrine factors released by immune cells, mainly GAMs, directly promote the proliferation and survival of GSCs (Roesch et al., 2018; Lin et al., 2023; Xuan et al., 2021; Khan et al., 2020). Furthermore, GAMs may induce a SC phenotype in NSCCs through both direct cell-cell interactions and the release of paracrine mediators (Silver et al., 2022; DeCordova et al., 2020; Alban et al., 2020; Roesch et al., 2018; Veglia et al., 2021). Conversely, GSCs contribute to maintain a tumor advantageous TIME through different mechanisms that include direct cell-cell interactions and release of paracrine factors and EVs. GSCs direct interactions are mainly established with GAMs, and result in the activation of their immunosuppressive phenotype and the inhibition of their phagocytic function. Signaling factors produced by GSCs attract Tregs and MDSCs and promote the accumulation of GAMs and their differentiation into de M2 immunosuppressive M2 type (Silver et al., 2022; Roesch et al., 2018; Lin et al., 2023; Xuan et al., 2021; Wu et al., 2010; Zhou et al., 2015). Finally, traffic of EVs produced by GSCs results in impaired CTL function and contribute to increase the recruitment of MDSCs. Remarkably, this intensive crosstalk between tumor and immune cells and, more specifically, between GSCs and TAMs may provide a novel strategy for GBM treatment, and disrupting this symbiosis has been shown to increase survival in experimental GBM models (Zhou et al., 2015; Wei et al., 2019).

## 6. Conclusion

Although stem cells represent one of the most promising frontlines in modern biomedical research, offering exceptional opportunities for novel therapeutical approaches, they may also be envisaged as a double-edged sword due to their harmful potential. The possibility of malignant transformation of either resident or therapeutically implanted SCs must be envisaged, especially in those types of tumors, like GBM, in which there is evidence regarding the involvement of NSCs in its origin. From a translational perspective, targeting stem cell plasticity could yield innovative therapies, but requires rigorous safety assessments to mitigate oncogenic risks. Future studies should prioritize in vivo models and clinical trials to harness these cells' regenerative power while distinguishing safe from risky ones.

## Ethics approval and consent to participate

Not applicable.

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## CRediT authorship contribution statement

Víctor M. Arce and Jose A. Costoya: Writing – original draft, Visualization, Funding acquisition, Conceptualization. Lara González-Rendo, Laura Porres-Ventín, Valentina González-Álvarez, Sabela Caamañó-Teixeira: Investigation, Visualization. Cristina Almengló, Rosa Señaris: Writing – review & editing, Visualization, Conceptualization.

## Consent for publication

All the authors agree with the submission and publication of this manuscript.

## Declaration of Competing Interest

The authors declare no conflict of interest.

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## Data availability

Not applicable.

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## Further reading

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**Rosa M. Señaris, MD, Ph.D.**, acts as Full Professor of Physiology at USC and Principal Investigator of the Neuroendocrinology, Metabolism and Cancer group at CiMUS-USC. With an MD and Ph.D. in Neuroscience from USC, plus postdocs at MRC Cambridge (UK), University of Aarhus (Denmark), and McGill University (Canada), she brings over 25 years of experience in energy homeostasis regulation, recent studies on thermosensation/TRPM8 in metabolism/obesity, and cancer cachexia therapies.

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