The tumour ecology of quiescence: Niches across scales of complexity

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A B S T R A C T

Quiescence is a state of cell cycle arrest, allowing cancer cells to evade anti-proliferative cancer therapies. Quiescent cancer stem cells are thought to be responsible for treatment resistance in glioblastoma, an aggressive brain cancer with poor patient outcomes. However, the regulation of quiescence in glioblastoma cells involves a myriad of intrinsic and extrinsic mechanisms that are not fully understood. In this review, we synthesise the literature on quiescence regulatory mechanisms in the context of glioblastoma and propose an ecological perspective to stemness-like phenotypes anchored to the contemporary concepts of niche theory. From this perspective, the cell cycle regulation is multiscale and multidimensional, where the niche dimensions extend to extrinsic variables in the tumour microenvironment that shape cell fate. Within this conceptual framework and powered by ecological niche modelling, the discovery of microenvironmental variables related to hypoxia and mechanosignalling that modulate proliferative plasticity and intratumor immune activity may open new avenues for therapeutic targeting of emerging biological vulnerabilities in glioblastoma.

1. Introduction

Glioblastoma (GBM) is a lethal disease with five-year survival rates of just 4% under current standard-of-care treatment [1]. Intratumor heterogeneity (ITH) is a cornerstone of GBM lethality. ITH in GBM is multidimensional, reflecting different stages of the cell cycle and stem-like cell states [2–4], genetic alterations [5,6], gene expression profiles [5,7], metabolic phenotypes [8–10], and histological patterns [11]. Further characterisation and subclassification of GBM using gene expression patterns [12–16] (e.g., *CDK4, PDGFRA, EGFR,* and *NF1*) have provided some correlations with treatment response [5]. However, regardless of the mutational status, phenotypic convergence is observed with cells harnessing many pathways and markers of deregulated neural stem and progenitor cells [4,17]. The plasticity and subclonal evolution of GBM cells [18] and their crosstalk with the tumour microenvironment

(TME) via epigenetic modifications [19–21] remain poorly understood, yet its study could reveal new biological vulnerabilities as new therapeutical targets.

Within the GBM cell population, a subgroup of quiescent glioblastoma cells with stem-like properties (GSCs) has the ability to re-enter the cell cycle from a resting stage, shaping the entire ecosystem of the tumour [22]. While the genetic and transcriptional heterogeneity of GSCs is clear [21,23,24], the extent to which the core stemness programme has plasticity or stability remains an area of active investigation [18,25,26]. That is further complicated by the fact that the stability of the stemness transcriptional and epigenetic programmes are known to shift during tumour development, evolution, and response to therapy. Such plasticity entails that, instead of a steep Waddington's landscape with deep valleys of differentiation with a static cellular hierarchy with GSCs at the apex, a cell transits through a rugged and evolving shallow

phenotypic landscape within its ecological tissue context. Hence, a GSC phenotype is part of a continuum of phenotypes for GBM cells , expressing characteristic transcriptional patterns [15,21]. For operational simplicity, this stem-like phenotype, GSCs, is categorised as a discrete state and therefore a subpopulation.

GSCs evade immune surveillance by entering a cellular arrest state [21,27–31] and have the capacity to drive tumour initiation, expansion, and recurrence *in vitro* and *in vivo* [4,32–34]. GSCs have characteristic transcriptional features. Expression profiling of quiescent GSCs revealed the upregulation of SAT1 and ID1 and the dysregulated expression of cyclin B1, CDKN1A and G0S2, which are important regulators of the cell cycle and tumour suppression [35]. GSCs quiescence and activation are mediated by BMP and TGFβ signalling, with downstream targets including ID1 and p21, respectively [35]. In addition, FOXG1, SOX2, and SOX9 are key transcription factors during neurodevelopment that are also commonly overexpressed in GSCs, suggesting parallels between normal neurological development and GBM [36–38]. The activation of proliferation and re-entry of quiescent GSCs into the cell cycle can also follow the use of temozolomide (TMZ) as a standard alkylating monotherapy as shown in transgenic mice bearing mutant *NF1*, *P53* and *Pten* mutations [34]. Notch and Sonic hedgehog pathways transcriptional activity is enhanced following TMZ exposure of CD133$^+$ GSCs, particularly Notch1, NCOR2, and GLI1 upregulation and CFLAR downregulation [39]. Mechanistically, the EGFR signalling pathway is the key pathway driving proliferation [40], among others such as TGFβ [41–43]. Any quiescence control should therefore regulate EGFR. For example, it has been shown that the re-entry of quiescent GSCs into the cell cycle is driven by LRIG1 and EGFR responsiveness by enabling high levels of EGFR protein but limiting signalling activation [44]. Collectively, these studies constitute extensive research into the intracellular mechanisms activating and preserving the quiescent state of GSCs. However, which and how extracellular signals shape cell quiescence are not fully understood. The knowledge of the complex multicellular context and extrinsic factors in the TME that drive and regulate the balance of GSC quiescence and proliferation is essential for understanding how tumour cell fate might be controlled therapeutically.

Tumour cells evolve and diversify within the TME [2,4,45,46]. Tumour-propagating clones display genetic and functional diversity, where competitive propagating advantages are associated with *TP53* mutation/EGFR amplification [47]. The diversification of individual clones may express unique proliferation and differentiation abilities [48]. This raises the question of how these varieties evolve within tumours and what selective pressures are exerted within the brain with different microenvironmental conditions (e.g., white matter, grey matter, blood vessels, meninges). GBM cell diversity is linked to emerging resistance to conventional anti-proliferative treatment such as TMZ [48], being an expected scenario in a heterogeneous population of cells along a continuum of states [21]. It is fascinating in light of overlapping niches and competition between clones, where the local extinction of TMZ-susceptible clones might open niche opportunities for expanding TMZ-resistant variants, which must be built upon an initially quiescent state. However, the solution is not straightforward. A continuous low-dose TMZ promotes GSCs and the secretion of PD-L1-containing exosomes, which in *in vivo* models promotes tumour growth and proliferation that ultimately can increase TMZ-resistance [49]. Increasing evidence suggests that a mesenchymal non-cycling state could be the resistant subpopulation of cells [50,51]. That subpopulation would evade immune response via epigenetic immunoediting processes following an immune attack, triggering a myeloid-affiliated transcriptional programme and leading to a reorganisation of the TME (e.g., recruitment of tumour-associated macrophages) [21]. Given such complexity, an integrative approach is required to consider the role of clone diversity, their coexistence, the conditions leading to tumour initiation in homoeostatic conditions, and the evolution in response to standard-of-care treatment as a selective pressure.

In this review, we present an eco-oncological approach under the contemporary notion of niche [52] to dissect GBM heterogeneity, with an emphasis on the modulation of the cell cycle and, in particular, quiescence. One property of this eco-oncological approach is its bi-directionality [51]. It is focused on the niche, biotic and abiotic environmental conditions, that shape GSCs' fitness and also on the impacts of GSCs on the TME. We argue that this, in addition to a quantitative ecological niche modelling, can shed light on understanding the different dimensions of ITH linked to the quiescent cell state (e.g., stemness [2,3], clone selection [53–55]) but also aspects related to the immune compartment, such as immune cell diversity [56,57], or T cell functioning [58]. The ultimate goal is to unveil the crosstalk between these variables and how all of these together orchestrate tumour evolution and resistance to treatment [59], allowing us to identify new vulnerabilities that can lead to further treatment options.

2. Heterogeneity in fitness and cell cycle regulation: proliferation and persistence

Persistent questions about ITH are, how is it generated and/or maintained? What is the link between the diversity observed at one scale (e.g., histological patterns) with variation at other scales, e.g., intracellular variation in transcriptional programmes? And how is that coordinated with the regulation of the cell cycle and quiescent states? Previous attempts [60–62] have used the concept of niche to answer that questions, but with a restricted and primarily descriptive application defining niches as histopathological features present across the tumour bulk described by the vascular arrangement (e.g., hyperplasia), presence of necrosis, tumour infiltration or pseudopalisading cells. In this review, we consider the contemporary concepts of fitness and ecological niche [52,63] and how this is connected to the cell cycle.

A cell's fitness has two components tightly linked to the cell cycle: survival and proliferation. In ecology, the concept of niche emerged to explain the fitness variation between organisms and how that shapes their coexistence in space and time. For tumour ecology, fitness is associated with cell proliferation or expansion and persistence over time.

Ecological niche has been defined following two main theories. One follows Grinnell [64] and Hutchinson's tradition [65], representing the niche as the set of conditions, biotic (e.g., symbiotic interactions) and abiotic (e.g., nutrients), necessary for organismal survival. Another development follows Elton [66], MacArthur [67,68], and Tilman's [69] approaches, defining niche as the impact of an organism on its environment, mainly linked to a consumer-resource paradigm with a more quantitative development. Both views converge into a contemporary concept of a niche [52], defined as "the joint description of the environmental conditions that allow a species to satisfy its minimum requirements so that the birth rate of a local population is equal to or greater than its death rate along with the set of per capita effects of that species on this environmental conditions". Replacing the word 'species' with 'cell' means that a niche relates to the set of biotic or abiotic conditions that define the boundaries of survival and proliferation as general processes with several mechanisms underpinning cell differentiation. This definition may convey the idea that the effect of the environment could only be assessed across generations of individuals, a Darwinian evolution paradigm. However, the environment also modulates the expression of traits during an individual's lifetime, i.e., its phenotype or state [70,71]. Hereafter, our approach is focused on the plasticity of cell's phenotypes, the navigation across a fate landscape and the environmental conditions where fitness is non-negative.

The niche is not fixed over time, and it is not restricted to a particular cell type or a histological pattern. Strictly speaking, the niche is an environmental space, biotic and abiotic, that can be mapped into a geographical area within the tissue (Fig. 1). Knowing that set of conditions for a particular cell phenotype will move us forward beyond the current paradigm of niches in tumour biology towards a functional understanding of how the TME shapes the cell phenotype and tumour
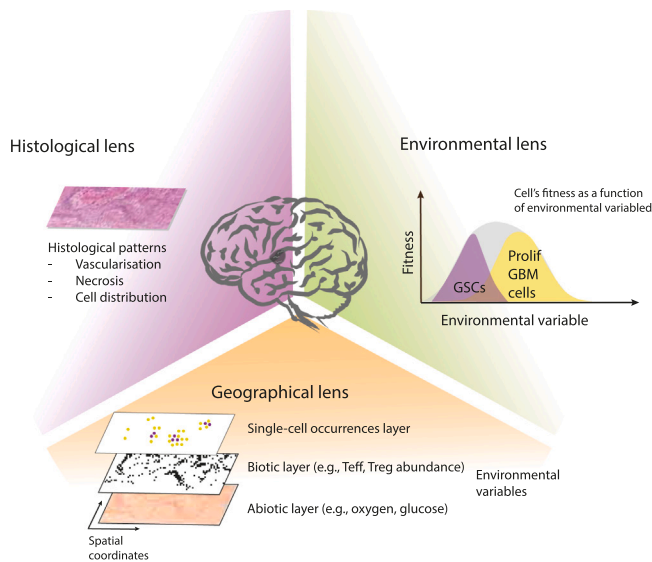
Fig. 1. Explaining patterns of coexistence between cell cycle stages through different lenses. Histological patterns detected in tumour samples emerge from the interaction of a myriad of biotic and abiotic variables associated with single-cell occurrences in a spatial/geographical context. These environmental variables are associated with cell fitness, where for example, GSCs and proliferating GBM cells may occupy different but complementary niche spaces along an environmental variable (e.g., GSCs more resistant to low oxygen conditions than proliferating GBM cells).

evolution. Our definition of niche for the cell context admits: (i) a cell can explore the environmental landscape within its niche, expressing different phenotypes [72]; (ii) that every cell type has a niche, and its breadth may quantify cell robustness to environmental fluctuations and plasticity; (iii) a particular region within the tumour can represent suitable conditions only for one cell phenotype or for more than one cell type (coexisting niches) explaining coexistence between different cell types; (iv) that two (or more) distant regions within a tumour can have the same niche for a cell type because they have the same environmental conditions.

We focus on the niche of GSCs, given their role in tumour initiation, progression, and response to therapy [4,32–34]. Although their presence in the neighbourhood of necrotic and vascular regions within the tumour tissue has been reported [73], there is a lack of an integrative way to unify transcriptional programmes with the dynamic TME. Hence, no definite niche dimensions have been proposed to elucidate the role of extrinsic variables on GBM cells' fitness, cell cycle regulation [46], or transcriptional circuitry associated with stemness [3,21].

3. Intratumor habitat suitability for cell-cycle states

The intratumoral distribution of GSCs, and in general of any cell, is shaped by the interaction of three intertwined elements: biotic interactions (cell-to-cell interactions), abiotic interactions (environmental factors, such as extracellular matrix or collagen), and dispersal or migration traits. This is known as the BAM framework in ecology (biotic, abiotic, and movement [74]). Hence, to further describe and mechanistically understand cell cycle stages, tumour evolution, vulnerabilities and prognostic value, it is necessary to analyse it from an integrative perspective such as the BAM framework. However, one of the biggest challenges is reproducing measures of the tumour ecology, the intratumor diversity and the distribution of cells to feed a quantitative niche theory of tumours and understand the spatial interactions of cells at a high spatial resolution.

3.1. Biotic constituents of niche: immune regulation of the cell cycle and crosstalk with immune cells' fitness

As parts of a community, other cell types can modulate the tumour cells' fate extrinsically (Fig. 2). Recent approaches have highlighted the ecological nature of cell-to-cell communication, for example, as parallels with predator-prey dynamics of effector T cells and tumour cells [75]. However, the role of immune cells is more complex than tumour surveillance, and other types of interactions (e.g., via regulatory T cells or myeloid cells) can subsidise tumour cell proliferation by immunomodulatory effects [76].

The consideration of intratumoral diversity and heterogeneity goes beyond cancer cell population. Also, it includes the diversity of immune phenotypes [48], their repertoire of T cell receptors [56] and their effect on tumour growth [77], for example, in response to immunotherapy [78–80]. In this sense, phenomena such as immune exhaustion are the result of a set of conditions that impact immune cells' fitness, producing, for example, an impaired production of effector cytokines (e.g., IL-2), IFN-γ, and TNF-α in T cells and a dysfunctional state of natural killers associated to glucose availability [81]. The effector T cell's fitness is likely driven by the coexistence with tumour cells and immunosuppressive cells and their associated cytokines (e.g., IL-10 and TGF-β) [58] or glucose availability [81] that control their effector capabilities. These conditions, biotic or abiotic, represent the lower limit for effective T cell immune surveillance in a niche space, therefore, their regulation is crucial for promoting intratumor immune activity [82].

The induction of a dormant phenotype in tumour cells inhabiting T-cell-enriched tumour regions was found to be driven mechanistically via Notch and IFN-γ signalling [17,83,84]. Furthermore, in a mouse model, it has been shown that transformed neural stem cells (NSCs) can induce quiescence in surrounding wild-type NSCs via Notch signalling-dependent manner through cell-cell interactions [85]. This mechanism is supported by the finding that Notch inhibition uncouples the growth of proneural glioma cells from their immune niche [84]. Endothelial cells also can promote the stem cell-like status via Notch, sonic hedgehog, and nitric oxide signalling pathways [86,87]. The Notch1 receptor maintains GSCs in perivascular, hypoxic, and white matter regions, suggesting a universal role of this pathway in regulating tumour cell-TME crosstalk [84,88]. Even for a single signalling pathway,
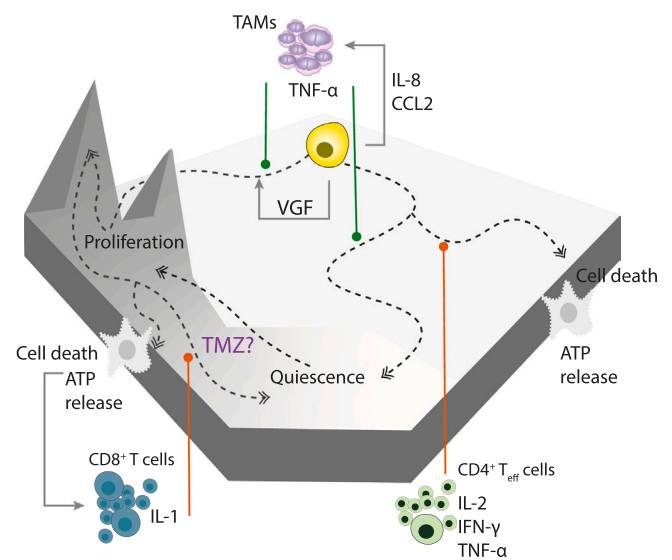

Fig. 2. Immune modulation of the GBM tumour cells' journey across the proliferative fitness landscape. The transition between stages of the cell cycle is accompanied by a complex network of cell-to-cell interactions, in particular with lymphoid and myeloid immune cells, through direct positive effects (orange lines) or indirect effects (green lines) on a process.

different cell types can shape the quiescent cell state via Notch, and that effect propagates through a complete network of cell interactions co-inhabiting the TME.

Nevertheless, the role of the immune system in promoting the adaptive transition of the cellular state of GSCs and how this relates to histological patterns remain unclear. We hypothesise that the induced tumour cell death in necrotic regions triggers a pro-inflammatory signal, activating innate immune cells and leading to T cell attack and/or macrophage and monocyte attack that could make the tumour cells go into dormancy, escaping the immune attack [89–91]. For example, it was demonstrated in a mouse model that CD8$^+$ T cells could induce lymphoma cell dormancy via IFN-γ signalling [92], while dormant tumour cells could express PDL1 to inhibit T cell attack in a murine model of acute myeloid leukaemia [93]. Following treatment such as TMZ, ATP could be released by the dying tumour cells, thus activating inflammasomes and stimulating the subsequent secretion of IL-1 by dendritic cells and cytotoxic CD8$^+$ T cells [94]. These active inflammatory signals can convert the proliferating GSCs to the immunosuppressive quiescence state, enabling tumour cells to evade immune surveillance. In addition, CXCL12 chemokine may promote GSCs state following TMZ treatment as shown *in vitro* [95]. The downstream CCL2 and SAA2 signalling may contribute to the entry into the therapy-mediated cellular dormancy. CXCL12 activates members of the MAP kinase family in gliomas via its G-protein-coupled receptors CXCR4 and CXCR7 to regulate the expression of CCL2 and SAA2. Subsequently, CCL2-CCR2 signalling that mediates tumour immune surveillance [96] and SAA2 signalling that promotes neutrophil adhesion to endothelial cells during inflammation is activated [97], helping tumour cells get rid of the TMZ. Hypothetically, CXCL12 may support the entry of the GBM quiescent state, hence tumour resistance to TMZ.

One of the main mechanisms of action for immune cells to eliminate tumour cells is by recognising the tumour antigens presented by the MHC molecules. Based on the Jedi mouse model on how other tissue stem cells, such as hair follicle stem cells (HFSC), evade the immune system [98], the downregulation of MHC class I (MHC-I) molecules play a key role in evading immune surveillance. In GSCs, the downregulation of MHC-I and the antigen-processing machinery components expressions are associated with the activation of the Wnt/β-Catenin pathway activation [99]. Additionally, the transcription factor Nlrc5, which regulates the expression of MHC-I, is also downregulated in quiescent HFSC, preventing the depletion of cells by T cells. In line with what Agudo and Merad [98] have shown, the expression of MHC-I molecules is reduced by the GSCs in multiple *in vitro* and *in vivo* models [100–102], eliciting evasion of the adaptive immune response, although NK cells can still perform their optimal cytotoxicity via receptor activation by corresponding ligands on the GSC, such as PVR and Nectin-2 [103]. In addition, co-culture experiments of CD70$^+$ glioma cells and human peripheral blood mononuclear cells have suggested that the interaction between CD70 on GBM cells and its receptor CD27 expressed on T and B cells induces T cell apoptosis upon immune cell activation [104], being one of the possible mechanisms of GBM tumour cells escaping immune response. The downregulation of MHC class II in microglia via Toll-like receptor 2 can also hinder the proliferation and activation of CD4$^+$ T cells [105]. In summary, the fine regulation of the antigen-processing machinery components is another crucial mechanism through which tumour cells, and in particular stem-like cells, can evade the immune response.

Furthermore, the immune system can also be manipulated by GBM cells via exerting the immunosuppressive signal. For instance, GBM cells secrete IL-8 and CCL2, recruiting GBM-associated macrophages to the tumour area and activating them to produce TNFα [106]. It is followed by the activation of endothelial cells, which support the metastasis of tumour cells and tumour progression [86,106]. Therefore, research has shown that a high TNFα expression correlates with a worse response to Bevacizumab in GBM patients and in mouse models. It is consistent with the observation that TNF-a overexpressed in glioma cells promotes

angiogenesis [107] and the activation of MHC class I molecules that help glioma cells escape from the immune surveillance via NK cell-mediated cytolysis [108,109]. In other systems, TNFα could induce pancreatic tumour dormancy with the IFN-γ signalling induced by CD4$^+$ T cells in a mouse model [110].

Receptor-ligand interactions between GBM tumour cells and immune cells might trigger the quiescent state and immune escape. Immune cells may provide ligands recognised by receptors that activate downstream pathways, such as BMP and TGF-β2 signalling pathways activated selectively to suppress immune responses [35]. TGF-B signalling pathway has implications related to tumour progression, for instance, by participating in the crosstalk between Smad/p38MAPK pathways [111] and also stabilising SOX9 promoting migration and invasion of glioma cells in xenograft tumours [42]. Additionally, suppression of TGF-β-RIII with specific siRNAs may induce a non-proliferative state as shown for U-373MG cells [43]. Subsequently, the expression of the cell cycle inhibitor p21 is increased, mediating the effect of BMP inducing reversible growth arrest [35]. Furthermore, we proposed that other immune cells and elements may also play a role in triggering the quiescence state of GSCs regulating relapse after standard-of-care interventions. For example, microglia cells are the immune cells that could decrease the invasion of patient-derived GBM via paracrine signalling [112]. Its inhibiting role in GBM invasion lowers the expression of NLR, NF-κB and TLR genes which encode the signalling pathway responsible for inflammation and tumour progression. Likewise, increasing IFN-γ concentrations increases MHC-2 expression *in vitro* [113], inducing cell death and inhibits the proliferation of GSC lines. Hence, it is likely that the alteration of the gene profiles in GBM stops the invasion and proliferation and would also switch their cellular programme to the quiescence state as does immunoediting. Collectively, this literature showcases that the survival of GSCs via immune escape is finely regulated by a network of interacting cells differentially triggering signalling pathways.

GSCs also remodel the TME affecting the fitness of other types of cells, for example, by producing high levels of proangiogenic factors, such as VEGF, that drive endothelial cell proliferation, survival and migration. Paracrine and autocrine secretion of VGF by GSCs support their survival and the proliferation of differentiated glioblastoma cells, hence tumour growth. VGF has two roles in the GBM hierarchy by promoting GSC survival and stemness *in vitro* and *in vivo* while also supporting differentiated cells' survival and inducing the secretion of brain-derived neurotrophic factors having positive feedback on VEGF secretion [114].

3.2. Abiotic constituents of niche: oxygen, glucose, and extracellular matrix

Hypoxia is one of the most conspicuous physical factors in GBM. Hypoxia attributed to insufficient blood supply is an unfavourable environment for tumour cells, playing a pivotal role in the heterogeneous TME, promoting tumour cell stemness and immunosuppression [115]. For instance, the anti-tumour activity of tumour-associated macrophages (TAMs) is decreased due to hypoxia-induced Nrp1 deficiency [116]. Subsequently, M1-like cytotoxic TAMs cannot immerse in the hypoxic tumour regions. Instead, it was proven by this *in vivo* mouse model that these TAMs are accumulated in the normoxic regions, leading to less vessel branching and the attenuated antitumour immune response induced by the Th1/CD8$^+$-T-cells-mediated release of IFN-γ. Similarly, Th1-derived IFN-γ has also been shown to induce macrophages to secrete the angiostatic chemokines CXCL9 and CXCL10, which may maintain micrometastases of GSCs in a dormant state. As we discussed, glucose availability in the TME can also modulate the immune activity of effector T cells [81], and interestingly GBM quiescence can be induced via autophagy during glucose starvation triggering chemoresistance through orchestration of cell metabolism, cell cycle, and fitness [117]. Hence, metabolic plasticity in a low glucose environment

can elicit immune escape and shift towards a quiescent cell state.

Fibrotic elements of the TME are other environmental variables in the modulation of quiescent states and tumour cell fitness across different tumour types [118–121]. Mechanosignalling pathways can modulate all the elements of a cell's fitness: growth, survival, invasion and treatment resistance [118,122–124]. For GBM in particular, it is suggested that the mesenchymal, stem-like phenotype observed in recurrent GBM could be induced via tension-mediated glyco-calyx–integrin feedback, suggesting novel in situ modulation of quiescent states and treatment strategies aiming to reduce TME tension [119]. Furthermore, collagen also can mediate immune activity (see a discussion in [125]), creating an immunosuppressive microenvironment for gliomas [126]. Since a bidirectional link between the biotic and abiotic elements is a quintessential aspect of GBM biology linking quiescent states, immune activity, and TME organisation, the next step is to map in the TME all these elements, quantifying multiscale relationships, and associate them with tumour progression and response to treatment.

4. A systematic view of the cell cycle regulation across scales of complexity

We have discussed how ITH is present at different aspects within the tumour boundaries. For instance, in tumour cells plasticity [26], the immune cell landscape [57,127,128] and overall in the cell distribution pattern and regional differences across the tumour [60]. This consideration summed to a spatial approach [129] allows, for example, to identify immune infiltrative regions and their association with different GBM subtypes [127,130]. An ecological approach can bring a systematic perspective to the processes, mechanisms, and patterns co-occurring within GBM, with organisational and spatial dimensions defining intratumor complexity in ecological terms (Fig. 3).

At the first level of the organisational dimension is the individual cell, the scale at which selection operates and where different facets of single-cell heterogeneity occur (e.g., cell cycle states, stemness, metabolic profiles). At the second level, a group of cells of the same type make a population of cells. Two main ideas are relevant here. The first one is that intrapopulation heterogeneity is expressed in the myriad of coexisting molecular programmes having, for example, structured populations with different proliferative phenotypes (proliferating and non-
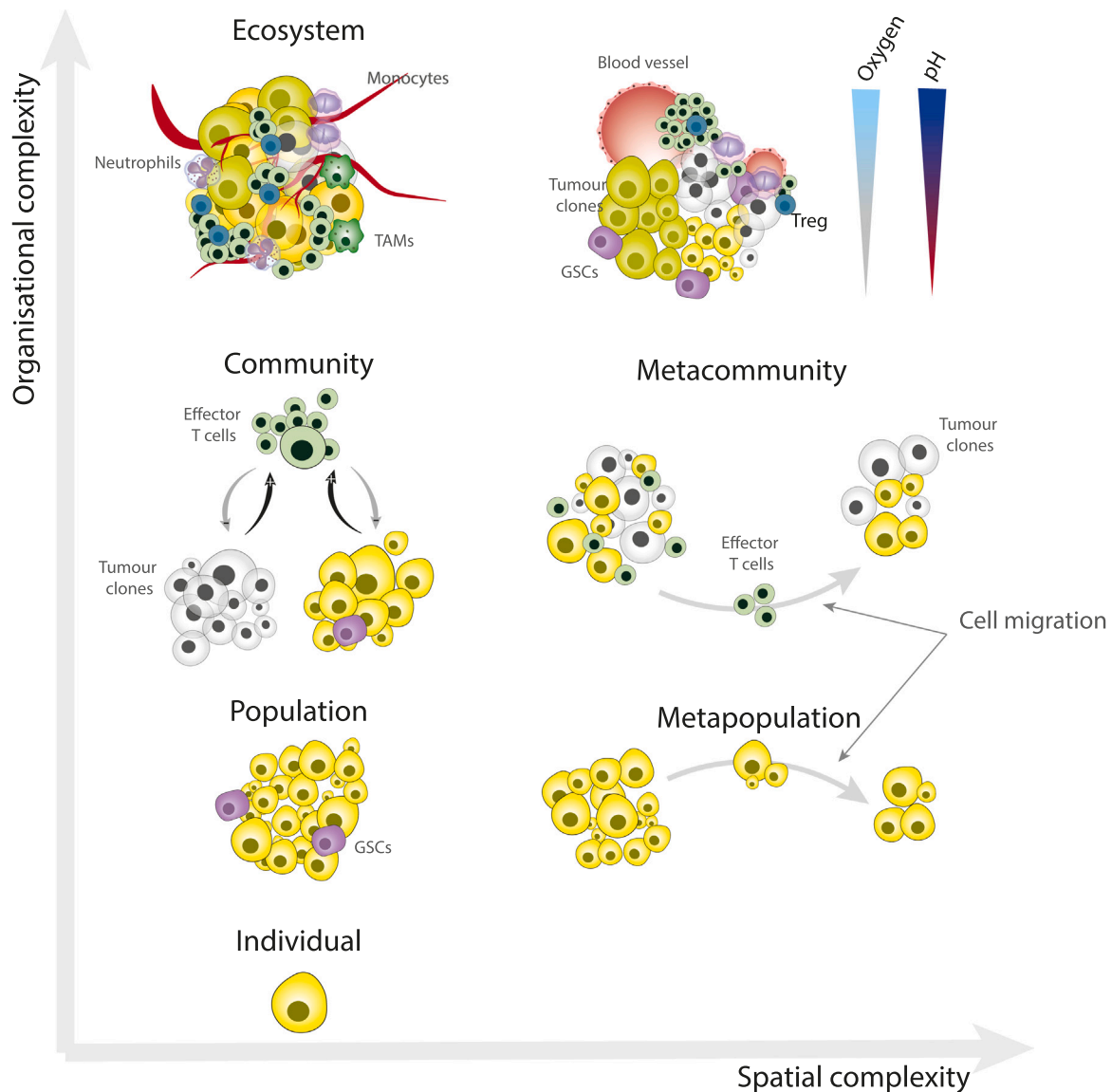

Fig. 3. A systematic view of intratumour heterogeneity through dimensions and scales. An ecological approach organises ITH along two dimensions according to the diversity of interacting elements and their spatial dimension.

proliferating tumour cells). The second idea is that population dynamics, the change in the number of cells over time, is one of the essential processes in tumour development and is what treatments often aim to control. Hence, understanding the mechanism of population regulation can contribute to understanding how tumour growth and cell turnover are regulated. For example, in an *NF1/P53/Pten* mutant mice model, when differentiated GBM cell populations are removed after TMZ monotherapy, treatment-resistant GSCs re-enter the cell cycle, highlighting the denso-dependency nature of GSCs activation [34,131]. The third level in the organisational dimension is represented by communities of cells from different lineages that coexist in space and time. For example, immune and tumour cells co-occurrence is a type of community. At the community scale, the emerging pattern resulting from the relationship between interacting cell types is what matters, and not just single pairwise interactions but the network of positive and negative feedbacks between different cell types (e.g., tumour cells, effector T cells, regulatory T cells, myeloid-derived cells). Thus, it is crucial to understand the associations between different elements of the TME. For example, when considering the interaction between treatment-persistent CD73 + macrophages with T cells [78], it is important to pinpoint that CD73$^+$ extracellular vesicles promote immunosuppression by inhibiting T-cell clonal expansion [132] and that the blockade of CD73 delays tumour growth by modulating the immune repertoire [79]. The fourth level of organisation is ecosystems, where the focus is on the feedback between the cellular (cell types) and the physicochemical elements of the TME (e.g., collagen, pH, oxygen). At this level, different cell types are affected, and affect, the abiotic components TME [119]. For example, Yin et al. [126] suggested various collagen-associated genes (COL1A1, COL1A2, COL3A1, COL4A1, COL4A2, and COL5A2) that could regulate the immunosuppressive microenvironment of gliomas. The relationship between diversity and its impacts on ecosystem functioning, resilience and robustness are particularly relevant for GBM biology since these links may mediate the response to immunotherapies, such as immune checkpoint inhibitors [80].

The second dimension is spatial complexity. Tumours are not a homogeneous or randomly distributed group of cells. A spatial dimension seeks to integrate that aspect of ITH. Spatially-resolved omics analyses have contributed to the understanding of the sharp changes occurring in the tumour-invasive-brain histological frontiers with prognostic value for GBM [51,133]. Recent investigations have revealed differential transcriptomics and proteomics patterns across histological features [134]. However, the mechanisms underlying the emergent spatial heterogeneity, including histological features, are unknown. At a more fundamental level, one can establish that they emerge from the interactions between the selective pressures of the TME on cell fitness and the cellular attributes, e.g., migratory ability. The migration of cells can connect different populations of cells within a tumour and enable short and long-range metastasis, conforming to what is known as metapopulations or metacommunities. These migrants, however, need to have suitable TME conditions to establish a persistent population. The unsuitability of the TME can also give rise to histological patterns, such as necrotic regions with pseudopalisading cells, which could represent a wave of migrating cells from a central hypoxic region after a vascular insult via vaso-occlusive and prothrombotic mechanisms [135]. Surprisingly, to avoid autophagy in hypoxic regions, plasticity in the mitochondrial shape of tumour cells is vital, being altered from a tubular shape to a doughnut shape, along with the upregulated gene expression of the calcium influx-related genes [136]. This highlights the importance of cell plasticity to prevail in what, in other contexts, could be unsuitable conditions for proliferation and survival.

5. Perspectives on niche modelling for GBM cell states

One alternative approach to quantify the relationship between individual cell states and environmental factors is via ecological niche modelling. In ecology, niche theory has guided the development of species distribution models (SDMs) [137], to extend the potential distribution of organisms beyond occurrences based on habitat suitability. Broadly, there are two groups of SDMs, correlative and mechanistic [138]. The most straightforward approaches are correlative SDMs or climate envelope models, which use statistical approaches to identify geographical areas where an organism could be found based on environmental similarity (e.g., temperature and precipitation) according to previously recorded individual occurrences (spatial coordinates). There are different correlative approaches to estimate the effect of environmental variables on species occurrences, optimising the search of parameters according to the type of input data (reviewed in [139]). For example, for presence-only data, there are climate envelope models such as Bioclim [140]. For presence-absence records, the offer includes logistic regressions, generalised linear models, boosted regression trees, and artificial neural networks [141], among others. For presence-background records, the most used approach uses maximum entropy, MaxEnt [142].

Nowadays, niche modelling is possible for tumour biology due to the emergence of spatially deconvoluted approaches to identify single-cell phenotyping and distribution within the tissue and in situ environmental variables, resulting in a recent application of SDMs to tumour ecology [143]. Of particular relevance are spatial omics which have not been applied extensively to GBM but in other tumour types, allowing investigations with high resolution into the mechanisms underlying cell fate and tumour progression [144]. These approaches require single-cell detection, which has been powered by artificial intelligence tools (e.g., [145,146]). The synergic action of those approaches, spatial omics and artificial intelligence tools, may help identify critical environmental variables that drive tumour evolution or, in the particular case of GBM, the modulation of quiescence. SDMs applied to the cellular scale will have a higher potential, for example, mapping and quantifying intratumor conditions - biotic and abiotic- for a particular proliferative stage (e.g., GSCs). Correlative SDMs could work as a baseline approach to develop more mechanistic models for cell niches (see mechanistic niche modelling [137]). That approach could significantly impact the identification of a series of phenomena linked to the coexistence of diverse cell types, diversification events, immunosuppression, and metabolic landscapes, among other patterns that nowadays puzzle us and impede us from moving forward towards improving patient care.

Some caveats and opportunities are worth mentioning. Computation pathology often deals with patient tumour samples where the movement of cells is impossible to recapitulate. However transcriptional signatures involved in EMT and ECM remodelling are present in GBM cells. The movement variable in the BAM framework defines motion as a trait that would allow, for example, GBM cells to migrate from the main tumour, escape the resection of the main mass, and proliferate in the resection margin influencing recurrence [147]. The movement would also allow mid-range colonisations to other parts of the brain, different to where the primary GBM originated by cells migrating through the normal parenchyma as described in 1940 by Sherer [148]. Finally, although less common, cell migration would also lead to extracranial metastases of GBM [149]. The movement consideration highlights that cells, e.g. GBM cells with a stemness signature, could be absent from some focal tissue despite having suitable biotic and abiotic conditions, just because the focal tissue is out of reach or cells have not migrated there yet. The same occurs within the tumour tissue, some regions in the tumour could have suitable (a)biotic conditions but we do not find GSCs there because they have not migrated there yet. That limitation accompanying traditional one-time snapshot-like tumour sampling highlights the need to advance in longitudinal data, and time-lapse data, whereas not possible in human patients, an opportunity to develop animal models. In addition, a way to work around those challenges is obtaining data from *in vitro* and *in vivo* models and incorporating them into hybrid models used in ecology (e.g., [150]) modelling cell movement on patient's tissue sections. However, this approach has essential assumptions about the parametrisation and

must be subjected to validation. That development would advance mechanistic niche modelling for tumour cells and their proliferative plasticity, by disentangling biotic and abiotic elements in the TME modulating the cell cycle.

6. Conclusions

The regulation of the cell cycle and the switch between proliferative and quiescent states are some of the central puzzles in GBM – and many other human cancers. A fraction of cells in a quiescent stem-like state can drive treatment resistance and recurrence. We have outlined the incredible complexity in cell cycle regulation, dynamics of the cell state transitions and TME, and how this occurs across multiple scales of organisation within the tumour. Through holistic and interdisciplinary efforts, progress is likely to come with the identification of intrinsic and extrinsic niche variables modulating cell fitness and spatial regulation of immune activity, leading to new treatment options for GBM.

The multiscale perspective entails that a myriad of factors changes dynamically in space and time, including immune activity as a central modulator of tumour evolution and the target of new treatment options [78,151]. ITH can be dissected across scales of organisational and spatial complexity. However, how is ITH at one level connected to another level? We think that an optimal approach is a question-oriented approach. For instance, we could ask how the proliferation of cells (a population scale phenomenon) is translated to the individual scale (likelihood of a cell to enter G0) or to the community scale, changing the local diversity of interacting cells, for example, by recruiting inflammatory immune cells. Nevertheless, the challenge is that as this is a question-oriented approach there is no definite answer to link all the processes across scales. Tumour ecology emerges not as a single answer, but instead as a framework and approach to answer and link scales.

CRediT authorship contribution statement

Simon P. Castillo: Conceptualization, Investigation, Writing - original draft, Writing - review & editing. **Felipe Galvez-Cancino:** Conceptualization, Investigation, Writing - review & editing. **Jiali Liu:** Investigation, Writing - review & editing. **Steven M. Pollard:** Funding acquisition , Writing - review & editing. **Sergio A. Quezada:** Funding acquisition , Writing - review & editing. **Yinyin Yuan:** Conceptualization, Funding acquisition, Supervision, Writing - review & editing.

Declaration of Competing Interest

The funders had no role in the writing of the manuscript, or the decision to submit the manuscript for publication. Y.Y. has received speakers bureau honoraria from Roche and consulted for Merck and Co Inc. The remaining authors declare no competing interests.

Data availability

No data was used for the research described in the article.

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