# QUIESCENCE, AN INDIVIDUAL JOURNEY

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| **Abstract:** | Quiescence is operationally characterized as a temporary and reversible proliferation arrest. There are many preconceived ideas about quiescence, quiescent cells being generally viewed as insignificant sleeping G1 cells. In fact, quiescence is central for organism physiology and its dysregulation involved in many pathologies. The quiescent state encompasses very diverse cellular situations depending on the cell type and its environment. This diversity challenges not only quiescence uniformity but also the universality of the molecular mechanisms beyond quiescence regulation. In this mini-perspective, we discuss recent advances in the concept of quiescence, and illustrate that this multifaceted cellular state is gaining increasing attention in many field of biology. |

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**ABSTRACT**

Quiescence is operationally characterized as a temporary and reversible proliferation arrest. There are many preconceived ideas about quiescence, quiescent cells being generally viewed as insignificant sleeping G1 cells. In fact, quiescence is central for organism physiology and its dysregulation involved in many pathologies. The quiescent state encompasses very diverse cellular situations depending on the cell type and its environment. This diversity challenges not only quiescence uniformity but also the universality of the molecular mechanisms beyond quiescence regulation. In this mini-perspective, we discuss recent advances in the concept of quiescence, and illustrate that this multifaceted cellular state is gaining increasing attention in many field of biology.

## Introduction

Unlike cell proliferation, cellular quiescence is often ill defined, considered as an inactive default state, and its biological relevance poorly acknowledged. However, an increasing amount of literature reveals that quiescence is central in many biological processes including major human diseases. In fact, quiescence is captivating, as it is diverse, multifaceted, and far from being a “sleeping” cellular state.

When speaking about cellular quiescence, it is crucial to define precisely what we are talking about. Quiescence is operationally defined as a temporary and reversible proliferation arrest, but conceptually, the difficulties arise from the rather loose notions of temporality and reversibility. First, one can wonder when does a cell that has ceased dividing should be considered as a *bona fide* quiescent cell? Although relevant, this question is probably not the way we should think about quiescence establishment, as quiescence entry is not a question of time but rather comes with specific molecular and cellular remodelling, that may even occur before cell proliferation cessation (see below). Second, a categorization based on reversibility separates quiescent cells - cells that keep their capacities to re-enter the cell cycle-, from senescent cells - cells that will never re-proliferate (Terzi et al. 2016). Yet, although this partitioning is practically helpful, it may be too simplistic. As examples, terminally differentiated neurons are in an apparently permanent cell cycle arrest, but can eventually re-proliferate following very particular stimulations (Sun and Buttitta 2017). Similarly, viable but non-culturable micro-organisms theoretically fall in the senescent cell category, but it is just because we have not found the way to make them divide (Oliver 2005). On the other side of the edge, quiescent cells face the damaging effects of age and with time, may lose their proliferation capacities and become senescent (Marthandan et al. 2014). Thus, the quiescence boundaries are floating.

In addition to these semantic issues, diverse forms of quiescence can be recognized. On the one hand, quiescence induced by macro- or micro-environmental conditions can theoretically be separated from quiescence that is coupled to differentiation as part of a programmed developmental plan (O’Farrell 2011; Fiore et al. 2018). On the other hand, various quiescence “degree” can be ascribed depending on cell’s “activities”. For example, upon quiescence entry, primary human fibroblasts continue to exhibit high flux in several metabolic pathways (Lemons et al. 2010; Valcourt et al. 2012) while other cells drastically reduced their overall metabolism and enter dormancy, a sort of extreme form of quiescence. Dormancy has been brilliantly discussed for unicellular

organisms (Lewis 2007; Jones and Lennon 2010; Rittershaus et al. 2013) and plants (Considine and Considine 2016; Velappan et al. 2017). Yet, while it is easy to acknowledge that spores are dormant since they undergo massive morphological changes (Huang and Hull 2017), this particular quiescent status is more debated in animals in which the frontiers of dormancy are more subjective (Rittershaus et al. 2013; Rocheteau et al. 2015). In sum, quiescence encompasses an infinite number of cellular situations depending on both the cell type and the environmental niche. This heterogeneity challenges the universality of molecular processes beyond quiescence establishment, maintenance and exit. Nevertheless, once the complexity of quiescence acknowledged, increasing evidences testify that quiescence is not a "frozen" default G1 state and that this cellular state is at the heart of most physiological and pathological biological processes.

**Quiescence is not an anecdotic cellular state.**

In the wild, quiescent micro-organisms are found in most ecosystems, from the human gut to soils or deep oceans. When microbes face environmental conditions that are unfavorable to division, they may adopt different strategies to persist in a quiescent state for months or even years (Corper and Cohn 1933). These "persisters" have been shown to be crucial not only to preserve biodiversity by limiting inter-species competition, but also for evolution (Jones and Lennon 2010; Shoemaker and Lennon 2018). Because they are non-dividing and therefore insensitive to many antibiotics, these quiescent cells are also a major threat for human health (Lewis 2007; Jones and Lennon 2010; Bojsen et al. 2017). The evolutionary success of unicellular species is related to their ability to sustain periods of nutrient starvation. Throughout evolution, the appearance of multicellular organisms is closely associated with the acquisition of the capacity to enter quiescence (O'Farrell 2011), even in a context in which cells are bathed in a nutrient-rich environment. In complex organisms, proliferation cessation at the right places and times is critical during development (O'Farrell 2011; Sun and Buttitta 2017). In adults, many cells within tissues are quiescent, but the archetype of quiescent cells is undoubtedly stem cells. A controlled balance between proliferation and quiescence is crucial for regenerating tissues after injuries, for hematopoiesis, immune response, renewal of epithelia, etc… and therefore for the entire body maintenance (Morrison and Spradling 2008; O'Farrell 2011; Chakkalakal et al. 2012; Rumman et al. 2015; Matson and Cook 2017; Fiore et al. 2018). Moreover, quiescence

establishment and exit, through the regulation of cell proliferation, have to be tightly controlled to avoid pathological situations including stem cell depletion and tumorigenesis (Orford and Scadden 2008; O'Farrell 2011; Cheung and Rando 2013; Dhawan and Laxman 2015). Interestingly, more and more evidences argue that micro-environment – both its composition and physical properties – plays a central role in regulating quiescence (Linde et al. 2016; Fiore et al. 2018). This is particularly true in the case of disseminated tumor cells that persist far from the primary tumor as undetectable quiescent individual cancer cells, the awakening of these malignant cells being thought to be the major cause of cancer recurrence (Aguirre-Ghiso et al. 2013; Sosa et al. 2014; Linde et al. 2016; Fiore et al. 2018). In addition to disseminated tumor cells, non-proliferating cancer cells - cancer stem cells - do exist within tumors and as such, resist to conventional anti-proliferative drug treatments (Chen et al. 2016; Fujimaki and Yao 2018; Vallette et al. 2018). Several strategies are currently under investigation to avoid cancer relapse and resistance, such as locking quiescent cancer cells in a non-proliferative state or forcing them to divide in the presence of chemotherapeutic agents (Chen et al. 2016). Thus, it urges to decrypt mechanisms beyond both quiescence regulation in healthy tissues and quiescence dysfunction in human pathologies.

**Quiescence establishment is not a passive arrest in G1.**

Quiescence establishment is often considered as a passive proliferation arrest at the restriction point in the G1 phase of the cell cycle. While the majority of quiescent cells do have a G1 DNA content, there are many examples of plants and animal cells that undergo endo-replication prior to quiescence entry and are therefore polyploidy (Sun and Buttitta 2017). Further, quiescent cells are not all necessarily arrested at the same "point" in G1 (Cooper 2003; Yao 2014) and several yeast species (Costello et al. 1986; Takeo et al. 1995), stem cells (Sutcu and Ricchetti 2018) and cancer cells (Drewinko et al. 1984; Pearl Mizrahi et al. 2016) can be found quiescent in G2. In fact, *S. cerevisiae* and *S. pombe* can survive in quiescence when they are artificially arrested in other cell cycle phase than G1 (Wei et al. 1993; Laporte et al. 2011). Nonetheless, several studies point to many signaling molecules acting in G1 as regulator of quiescence. This includes the tumor suppressor p53 and Rb, the cyclin-dependent kinase inhibitors p21 and p27, and several transcription factors such as FoxO (Cheung and Rando 2013; Rumman et al. 2015; Sun and Buttitta 2017; Matson and Cook 2017;

Miles and Breeden 2017). Yet, inactivation of these pathways does not necessarily hamper quiescence establishment (Matson and Cook 2017). Importantly, an artificial prolonged G1 arrest does not recapitulate quiescence establishment both in yeast and mammals (Coller et al. 2006; Laporte et al. 2011). In fact, accumulating evidences indicate that quiescence establishment involves the active repression of G1 progression genes (Litovchick et al. 2007; Sang et al. 2008; Yao 2014; Matson and Cook 2017) and the expression of genes which signature vary depending on the signal that has triggered quiescence entry (Coller et al. 2006; Klosinska et al. 2011). Further, expression of particular miRNAs, the RNA interference machinery, specific histone marks and telomere rearrangements have been shown to regulate quiescence (Cheung and Rando 2013; Roche et al. 2017; Maestroni et al. 2018), suggesting that this cellular fate is actively established and maintained. In addition, quiescence entry is accompanied by many specific remodelling, including chromatin reorganization, protein re-localization and cytoskeletal re-arrangements (Sagot and Laporte 2018). These large-scale cellular manoeuvres may be a way to avoid the damaging effects of age or to improve the fitness of quiescence exit.

Finally, studies in mammals suggest that the decision to enter quiescence is taken prior to the proliferation arrest in G1, in the G2 phase of the previous cell cycle. This forecast cell fate involves a bifurcation in the levels of Cdk2 activity and a Rb-E2F bi-stable switch (Hitomi and Stacey 1999; Chassot et al. 2008; Spencer et al. 2013; Naetar et al. 2014; Dhawan and Laxman 2015; Sun and Buttitta 2017; Matson and Cook 2017). Interestingly, in yeast, the decision seems to be made several cell cycles before proliferation cessation (Lillie and Pringle 1980; Zhang and Cao 2017; Argüello-Miranda et al. 2018). Therefore, quiescence establishment is a multifaceted anticipated process for which a G1 arrest is not mandatory, thereby questioning the use of the term “G0”.

**Quiescence is not a “frozen” cellular state**

Are all quiescent cells “frozen”? As stated above, depending on the cell type, quiescent cells metabolic activities drastically vary. Although it may be slowed down, a minimal rate of protein synthesis is required for survival in quiescence. Besides, an increased mRNA stability has been observed in many quiescent cell types (Gray et al. 2004; Valcourt et al. 2012; Rittershaus et al. 2013). Quiescent cells also preserve both membrane potentials and energy production, the maintenance of ATP synthesis, either

by respiration or fermentation, being essential to avoid cell death (Rittershaus et al. 2013). Further, quiescence is not necessarily associated to a general slowdown of all metabolic fluxes (Sauer et al. 1999; Lemons et al. 2010; Klosinska et al. 2011; Valcourt et al. 2012; Rittershaus et al. 2013), some specific pathways being more active in quiescent cells than in their proliferating counterpart (Lemons et al. 2010; Chen et al. 2012). Hence, quiescent cells are not all asleep.

In fact, many quiescent cells seem to be poised, ready to re-enter the cell cycle the more efficiently as possible (Cheung and Rando 2013). In quiescent *S. cerevisiae*, the RNA polymerase II is stalled onto specific promoters, ready to fire genes required for the early steps of G1/S progression (Radonjic et al. 2005). A similar mechanism may exist in stem cells, in which epigenetic histone marks could be functionally important for cell cycle re-entry (Cheung and Rando 2013). Moreover, some transcription factors and several quiescence specific cellular reorganization such as the formation of proteasome storage granules and stable microtubule bundles are critical for quiescence exit (Sagot and Laporte 2018; Kuang et al. 2018). More generally, cellular machineries essential for proliferation such as cytoskeletons or macromolecular complexes may be stored in quiescent cells as immediately mobilizable reservoir (Sagot and Laporte 2018). Further, difference in responsiveness have been observed in both yeast and several mammalians quiescent cells, including stem cells. Indeed, within a clonal cell population, individual quiescent cells can exhibit significantly different swiftness in re-entering proliferation (Rodgers et al. 2014; Dhawan and Laxman 2015; Tierney and Sacco 2016; Wang et al. 2017; Laporte et al. 2017). Finally and importantly, it has been proposed that quiescence duration influences individual quiescent cell properties and that young quiescent cells do not have the same features and abilities that cells that have been quiescent for longer period. In yeast and fibroblast, this “deepening” of quiescence has been shown to negatively influence quiescence exit efficiency (Yao 2014; Wang et al. 2017; Kwon et al. 2017; Laporte et al. 2017). Thus, quiescent cell properties change with time.

As a conclusion, quiescent cells properties are very different depending on the cell type, its environment, and the time spend in this non-proliferating state. Even clonal cell population in a given niche should be considered as a sum of heterogeneous individualities. It may be unrealistic to believe that universal properties shared by all quiescent cells could exist and that the molecular mechanisms beyond quiescence

regulation are all evolutionary conserved. Yet, quiescence in its biological significance, its diversity and its complexity is a fascinating cellular state, and we have just uncovered the very tip of the iceberg. Many more is to come…

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