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p21 as an essential regulator of neurogenic homeostasis in neuropathological conditions

Valentina Mastrorilli, Stefano Farioli-Vecchioli*

Adult neurogenesis is a highly dynamic process that leads to the production of new neurons from a population of quiescent neural stem cells (NSCs). In response to specific endogenous and/or external stimuli, NSCs enter a state of mitotic activation, initiating proliferation and differentiation pathways. Throughout this process, NSCs give rise to neural progenitors, which undergo multiple replicative and differentiative steps, each governed by precise molecular pathways that coordinate cellular changes and signals from the surrounding neurogenic niche. The ultimate goal of this complex genetic machinery is to ensure a continuous supply of new mature and functionally active neurons to pre-existing neural circuits, while also maintaining the neural stem cell pool as intact as possible, both under physiological conditions and in response to positive or negative external stimuli (Niklison-Chirou et al., 2020). In fact, disruption of this delicate balance can lead to neurogenic deficits or depletion of the NSCs pool. In this context, p21 has been identified as a key regulator of two pivotal processes in adult neurogenesis: the transition between quiescence and activation of NSCs, and the progression of progenitor proliferation (Maeda et al. 2023).

Two recent works have highlighted additional roles of p21 expression in regulating adult hippocampal neurogenesis in neuropathological conditions (**Figure 1**). Chiani et al. (2024) demonstrated that p21 played a crucial role in coordinating the hippocampal neurogenic response in a post-injury context by maintaining the integrity of the NSCs pool, while Wang et al. (2024) have emphasized how this gene, by interacting with oxidative stress-associated gene, was able to mediate the effect of corticosterone (CORT) on the hippocampal neurogenesis deficits.

In the first study, the authors used a new murine model of conditional deletion of p21 in NSCs, while in the other p21 was overexpressed through adenoviral infection of the dentate gyrus (DG). Both studies converge on the importance of this gene in regulating the homeostasis of neurogenic processes in neuropathological conditions. Furthermore, these papers significantly broaden the overall understanding of p21 as an essential gene for regulating both the proliferative steps of NSCs and the differentiation dynamics of NSCs and neuroblasts, intimately interacting with the molecular pathways that orchestrate the cell cycle. Indeed, in the work of Chiani et al. (2024), the authors observe that, under physiological conditions, the conditional deletion of p21 in NSCs following Tamoxifen administration induces an increase in the recruitment of quiescent NSCs into the cell cycle. This event, in turn, enhances proliferative and differentiative processes within the hippocampal neurogenic niche leading to a massive increase in adult neurogenesis and to an improvement of mnemonic tasks dependent on hippocampal neurogenesis. This event is most likely due to an upregulation of key players of the cell cycle, such as cyclin D2, involved in the positive mitotic progression of NSCs. Supporting this hypothesis, a study has demonstrated that the over-expression of the protein complex cyclin D1/CDK4 induces a profound pro-neurogenic effect in the murine Dentate Gyrus (Artegiani et al., 2011). Another important aspect to consider is that the increased proliferation of p21-depleted NSCs does not involve replicative stress processes typically induced by hyper-proliferation, as observed in postnatal p21 KO mice, where a rapid depletion of the pool of hyper-proliferating NSCs occurs (Kippin et al., 2005). In fact, within postnatal neurogenic niches, the proliferative processes of NSCs and neural progenitors are characterized by a shorter cell cycle and a slower exit from the cycle compared to what is observed in adult neurogenic niches. Consequently, the p21 deletion during the post-natal period leads to a higher proliferative rate leading to replicative stress mechanisms followed by rapid depletion of the pool.

Chiani et al. (2024) demonstrated that in the adult hippocampus an exhaustion of the pro-neurogenic processes due to p21 depletion only 100 days after Tamoxifen administration. More importantly, no long-term depletion process of the NSC pool was observed. Indeed, the expression of p21 in adult NSCs may appear redundant, or even negative for the neuroplastic potential of adult hippocampal neurogenesis, a kind of "handbrake" that limits the source of adult NSCs within the DG. However, observations made in a post-injury context clearly suggest that the expression of this gene is essential for regulating the neurogenic steps following brain damage (Chiani et al., 2024). In fact, it is known that a mild/moderate traumatic brain injury (TBI) can stimulate hippocampal neurogenic processes as part of the broader neuro-reparative response that is established in the brain following cortical damage (Marzano et al. 2022). But what happens instead in the absence of p21 in NSCs following TBI? Chiani and collaborators addressed this question by demonstrating that an initial powerful increase in the activation and proliferation processes of NSCs is followed by a rapid and dramatic depletion of the pool that leads to a long-term impairment of adult neurogenesis and hippocampal-dependent mnemonic skills. These events lead us to make two general considerations. The first one is that the expression of p21 is not essential under physiological conditions, but rather when an external pro-neurogenic stimulus drives an increase in the activation and proliferation of quiescent NSCs. In these situations, p21 finely modulates the molecular pathways that orchestrate the progression of the various stages of the cell cycle, preventing excessive activation/proliferation of NSCs. This excessive proliferation leads to depletion of the NSC pool and impairment of neurogenesis. The second consideration arises from the hypothesis that within the hippocampal

Figure 1 | P21 modulation in pathological conditions alters hippocampal neurogenic processes.
p21 plays a key role in regulating adult hippocampal neurogenesis by controlling the transition between quiescence and activation of NSCs and the proliferation of progenitors (left box). However, recent studies indicate p21 as a key homeostasis regulator of neurogenic response in neuropathological conditions (right box). Created with BioRender.com. AAV: Adeno-associated virus; CORT: corticosterone; NSCs: neural stem cells; TBI: traumatic brain injury.

neurogenic niche, there is a common mechanism - likely involving p21 and other genes expressed during the cell cycle - capable of maintaining the activation/proliferation rate of NSCs below a certain threshold. If this threshold is exceeded, it leads to a progressive exhaustion of the NSC pool. It is as if a compromise has been reached in the hippocampal neurogenic niches, where, at the expense of slightly reduced neuroplasticity, the integrity of the NSC pool is preserved, ensuring the availability of potentially inducible NSCs in cases where a pro-neurogenic stimulus threatens the primary source of new hippocampal neurons.

Furthermore, a recent study elegantly describes how a moderate TBI induces a specific increase in neurogenesis at the expense of astrogliogenesis, originating from common neural precursors, the Radial Glial-like NSCs (Bielefeld et al. 2024). In this study, the Authors identified six differentiation stages of NSCs (N-stage 1–6), some of which (N-stage 1, 2, 4, and 5) are preferentially increased following TBI. Regarding the post-injury proliferative dynamics, the study characterized two main phenomena: (1) a significant increase in proliferation within the NSC-stage 2 population; (2) up-regulation of the pro-proliferative gene Ppp1r14b in RG-like NSCs, which plays a crucial role in the post-injury activation and proliferation of these cells. Although the involvement of cell cycle-regulating genes, such as p21 or cyclins, in cell fate dynamics and proliferation within NSCs is not mentioned, this study confirms that TBI induces a series of gene changes that modify the NSCs fate decision and transition rather than their developmental stages.

In the second work we considered, the new role attributed to the p21 gene in the hippocampal neurogenic niche is framed within a context characterized by phenomena associated with CORT-induced anxiety states (Wang et al. 2024). In this study, the authors discovered that chronic treatment with CORT induces an increase in the expression of p21 in the hippocampal dentate gyrus, which interacts with oxidative stress-related genes and mediates the negative impact of CORT on adult neurogenesis and hippocampus-mediated emotional responses. Confirmation of involvement of p21 in the CORT-mediated pathway comes from the overexpression of p21 in the DG that partially recapitulates some of the phenotypes induced by chronic exposure to CORT, including impairment of adult hippocampal neurogenesis, reactive oxygen species (ROS) accumulation, and anxiety-like behavior. Moreover, the finding that antioxidants partially mitigate p21 upregulation-induced hippocampal dysfunction and anxiety-like behaviors suggests a direct correlation between p21 over-expression and ROS accumulation. The molecular mechanisms underlying these interactions are still poorly understood, although it has been hypothesized that ROS accumulation following p21 up-regulation may be due to p21-induced mitochondrial impairment with a consequent generation of ROS through a sequential signaling cascade (Passos et al. 2010). Alternatively, it has been suggested that ROS-induced DNA damage results in p53 activation, which in turn up-regulates p21, creating a reinforcing feedback loop formed by p21-ROS-p53 (Liu et al. 2008). In conclusion, Wang et al. (2024) suggest that p21 represents a key modulator in hippocampal anxiety-related processes, capable of inducing cell cycle arrest and oxidative stress in response to elevated CORT levels.

While previous studies have hypothesized a regulatory role of p21 in hippocampal neurogenesis during inflammatory processes (Zonis et al. 2013) and in response to antidepressant treatment (Pechnick et al. 2011), these last two researches greatly expand the molecular and cellular landscape within which this gene contributes to maintain a cellular balance essential for the correct functioning of hippocampal neurogenesis. As evidence of this hypothesis, modifications in p21 expression within the hippocampal neurogenic niche have profound effects not only on the proliferative and differentiative dynamics of newly generated NSCs and progenitor cells but also on hippocampal functionality, influencing learning, memory, and emotional behavior. Consequently, the identification of p21 as a hub gene in key hippocampal neurogenic pathways highlights the pivotal role of this gene in counteracting the anti-neurogenic effects of different neuropathologies, including mood disorders and brain injuries.

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Valentina Mastrorilli, Stefano Farioli-Vecchioli*
Institute of Biochemistry and Cell Biology, IBBC, CNR, Monterotondo, Rome, Italy
***Correspondence to:** Stefano Farioli-Vecchioli, PhD, stefano.farioli-vecchioli@cnr.it.
https://orcid.org/0000-0001-7059-7779 (Stefano Farioli-Vecchioli)
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p21 作为神经病理条件下神经源性稳态的重要调节因子
文章特色分析

一、文章重要性

1. 揭示 p21 在神经稳态中的双重角色

p21 长期以来被认为是细胞周期调控蛋白，但本文系统性地阐述了它在生理与病理条件下对神经干细胞（NSCs）行为的不同影响，特别是在创伤性脑损伤（TBI）和皮质酮（CORT）诱导的焦虑模型中，p21 起到“刹车”作用，防止 NSCs 过度激活与耗竭。

2. 连接神经发生与行为表现

文章不仅关注细胞层面的神经发生变化，还将其与学习记忆能力、情绪行为等功能表现联系起来，强调了 p21 在维持海马功能完整性中的核心地位。

3. 为神经再生与修复提供新靶点

通过阐明 p21 在神经病理条件下调控神经发生的机制，本文为开发针对神经退行性疾病、脑损伤或情绪障碍的治疗策略提供了潜在分子靶点。

二、创新性特色

1. 整合多模型研究，揭示 p21 的病理特异性功能

- 结合了条件性基因敲除（Chiani et al., 2024）与腺病毒过表达（Wang et al., 2024）两种实验策略，从正反两方面验证 p21 在不同病理情境下的作用。
- 揭示 p21 在生理状态下非必需，但在病理刺激下不可或缺，具有“情境依赖性”调控特性。

2. 提出“稳态阈值”假说

文章提出海马神经发生存在一个由 p21 等基因维持的激活/增殖阈值，超过该阈值将导致 NSCs 耗竭。这一概念为理解神经发生调控提供了新框架。

3. 关联氧化应激与神经发生障碍

首次系统地将 p21 与 CORT-ROS-p21-p53 反馈环路联系起来，解释其在焦虑相关神经发生障碍中的作用，拓展了 p21 在情绪障碍中的分子机制。

三、对学科的启示

1. 重新评估 p21 在神经发生中的功能定位

传统上 p21 被视为抑制神经发生的因子，本文则强调其在维持长期神经源性稳态中的保护性作用，尤其是在应对病理刺激时的“守护者”角色。

2. 强调神经发生调控的“动态平衡”理念

文章倡导在神经再生研究中应更加重视稳态机制，而非单纯促进或抑制神经发生，提示未来治疗策略需兼顾“促再生”与“防耗竭”。

3. 推动跨病理模型的整合研究

通过同时探讨 TBI 和 CORT 模型，文章展示了不同神经病理条件下共有调控机制的存在，鼓励未来研究在更广泛的疾病背景下考察神经发生的共同分子基础。

4. 为精准神经再生医学提供思路

p21 作为“枢纽基因”，其表达水平可能成为评估神经发生状态、预测治疗反应的生物标志物，也为开发病理阶段特异性干预策略奠定基础。

总结

本文通过整合最新研究成果，系统阐述了 p21 在神经病理条件下调控海马神经发生稳态的核心机制，不仅在理论上深化了对神经发生调控网络的理解，也在转化医学层面为神经再生与精神疾病治疗提供了新视角。其创新之处在于将 p21 从传统的细胞周期调控因子提升为神经稳态的关键调节者，具有重要的学科引领价值。