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Reactive Neuroblastosis in Huntington’s Disease: A Putative Therapeutic Target for Striatal Regeneration in the Adult Brain

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The cellular and molecular mechanisms underlying the reciprocal relationship between adult neurogenesis, cognitive and motor functions have been an important focus of investigation in the establishment of effective neural replacement therapies for neurodegenerative disorders. While neuronal loss, reactive gliosis and defects in the self-repair capacity have extensively been characterized in neurodegenerative disorders, the transient excess production of neuroblasts detected in the adult striatum of animal models of Huntington’s disease (HD) and in post-mortem brain of HD patients, has only marginally been addressed. This abnormal cellular response in the striatum appears to originate from the selective proliferation and ectopic migration of neuroblasts derived from the subventricular zone (SVZ). Based on and in line with the term “reactive astrogliosis”, we propose to name the observed cellular event “reactive neuroblastosis”. Although, the functional relevance of reactive neuroblastosis is unknown, we speculate that this process may provide support for the tissue regeneration in compensating the structural and physiological functions of the striatum in lieu of aging or of the neurodegenerative process. Thus, in this review article, we comprehend different possibilities for the regulation of striatal neurogenesis, neuroblastosis and their functional relevance in the context of HD.

Keywords: Huntington’s disease, adult neurogenesis, striatum, reactive neuroblastosis, doublecortin

INTRODUCTION

Huntington’s disease (HD) is an adult onset, progressive neurodegenerative syndrome that has clinically been characterized by chorea, dementia and psychiatric illness (Walker, 2007). Historically, symptoms of chorea had been observed by many physicians (Lanska, 2010), while George Huntington portrayed the clinical symptoms and provided the evidence for the hereditary nature of HD in 1872 (Huntington, 1872; Lanska, 2000). Since then, an enormous scientific progress has been made in understanding the biochemical, molecular genetics and pathological basis of HD worldwide (Wexler et al., 2004; Bates, 2005; Moily et al., 2014). In 1983, the HD Collaborative Research Group, under the direction of Nancy Wexler, successfully mapped the defective gene responsible for HD to chromosome 4p16.3 (Gusella et al., 1983). In 1993, the disease pathogenic mutation has been recognized as a polymorphic CAG-repeat expansion in the exon 1 of the HD
OB (Lois and Alvarez-Buylla, 1994; Doetsch et al., 1999; scaffold platform for the migrating neuroblasts towards the brains, the glial tube structure of the RMS provides a human brain are yet to be validated. In non-primate mammalian evidence for the migration of neuroblasts and mechanisms from suicide subjects (Maheu et al., 2015). However, the neuroblasts in the SVZ-OB path in the post-mortem brains evidence for the occurrence of doublecortin (DCX) positive (et al., 2014). A recent report by the Mechawar group provided ongoing subject of debate (Kirschenbaum et al., 1999; Pagano et al., 2004). Besides, adult neurogenesis has also been characterized in neurogenesis and migration of neuroblasts in the forebrain of adult subjects as it represents a possible self-regenerative mechanism of the neurodegenerative conditions including HD (Curtis et al., 2003; Kanda samy et al., 2010; Ernst et al., 2014). Here, several preclinical models of HD have been generated to investigate the roles of mutant HD gene in HD pathogenesis. The regulation of neurogenesis in NSC niches has been evaluated in R6/1 (Lazic et al., 2006), R6/2 (Kohl et al., 2007), N171-82Q (Duan et al., 2010)—genetic rodent models and in the quinolinic acid injection-induced acute rat model of HD (Tattersfield et al., 2004). Besides, adult neurogenesis has also been characterized in post-mortem brains of human HD subjects (Curtis et al., 2003; Low et al., 2011; Ernst et al., 2014). Notably, the proliferative potential of NSCs is reduced specifically in the hippocampus in most genetic models of HD (Lazic et al., 2006; Kohl et al., 2007; Kandasamy et al., 2010; Simpson et al., 2011), but no changes in the hippocampal NSC proliferation were observed in the post-mortem tissue of HD patients (Low et al., 2011). While the NSC proliferation rate was reduced in the hippocampus, the overall cell proliferation was unaltered in the SVZ of R6/1 (Lazic et al., 2006), R6/2 (Kohl et al., 2007), YAC128 (Simpson et al., 2011) and TgHD (Kandasamy et al., 2010)—genetic rodent models and in the quinolinic acid injection-induced acute rat model of HD (Tattersfield et al., 2004). Besides, adult neurogenesis has also been characterized in post-mortem brains of human HD subjects (Curtis et al., 2003; Low et al., 2011; Ernst et al., 2014). Notably, the proliferative potential of NSCs is reduced specifically in the hippocampus in most genetic models of HD (Lazic et al., 2006; Kohl et al., 2007; Kandasamy et al., 2010; Simpson et al., 2011), but no changes in the hippocampal NSC proliferation were observed in the post-mortem tissue of HD patients (Low et al., 2011). While the NSC proliferation rate was reduced in the hippocampus, the overall cell proliferation was unaltered in the SVZ of R6/1 (Lazic et al., 2006), R6/2 (Kohl et al., 2007), YAC128 (Simpson et al., 2011) mouse models and of early stage tgHD rats when compared to that of respective control animals (Kandasamy et al., 2010). In contrast, cell proliferation

NEUROGENESIS AND NEUROBLASTOSIS IN THE ADULT HD STRIATUM

Physical exercise and environmental enrichment paradigms have been shown to positively influence hippocampal neurogenesis in the healthy brain (Kempermann et al., 1997; van Praag et al., 1999). While the SVZ of the adult brain is highly refractory to external stimuli in the physiological state (Brown et al., 2003), acute neurological deficits like, cerebral stroke (Kokaia et al., 2006) and neurotoxic lesions (Winner et al., 2006) have been shown to trigger the multiplication of a subset of NSC progenies in the SVZ and the migration of these cells towards the incapacitated brain regions. Thus, enormous attempts have been made to characterize the regulation of neurogenesis and migration of neuroblasts in the forebrain of adult subjects as it represents a possible self-regenerative mechanism of the neurodegenerative conditions including HD (Curtis et al., 2003; Kokaia et al., 2006; Kohl et al., 2007; Kandasamy et al., 2010; Ernst et al., 2014). Here, several preclinical models of HD have been generated to investigate the roles of mutant HD gene in HD pathogenesis. The regulation of neurogenesis in NSC niches has been evaluated in R6/1 (Lazic et al., 2006), R6/2 (Kohl et al., 2007), N171-82Q (Duan et al., 2008), YAC128 (Simpson et al., 2011) and TgHD (Kandasamy et al., 2010)—genetic rodent models and in the quinolinic acid injection-induced acute rat model of HD (Tattersfield et al., 2004). Besides, adult neurogenesis has also been characterized in post-mortem brains of human HD subjects (Curtis et al., 2003; Low et al., 2011; Ernst et al., 2014). Notably, the proliferative potential of NSCs is reduced specifically in the hippocampus in most genetic models of HD (Lazic et al., 2006; Kohl et al., 2007; Kandasamy et al., 2010; Simpson et al., 2011), but no changes in the hippocampal NSC proliferation were observed in the post-mortem tissue of HD patients (Low et al., 2011). While the NSC proliferation rate was reduced in the hippocampus, the overall cell proliferation was unaltered in the SVZ of R6/1 (Lazic et al., 2006), R6/2 (Kohl et al., 2007), YAC128 (Simpson et al., 2011) mouse models and of early stage tgHD rats when compared to that of respective control animals (Kandasamy et al., 2010). In contrast, cell proliferation

MIGRATION OF NEUROBLASTS IN THE HEALTHY ADULT FOREBRAIN

The subventricular zone (SVZ) is a prime neuropoietic niche of the brain responsible for the postnatal neurogenesis in the telencephalon (Doetsch et al., 1997, 1999). In the adulthood, the SVZ continues to harbor a heterogeneous population of neural stem cells (NSCs) that generates polarized neuroblast progenies, migrating through the rostral migratory stream (RMS) into the olfactory bulb (OB), where they terminally mature into functional interneurons (Doetsch et al., 1997, 1999; Gritti et al., 2002; Ming and Song, 2011). While neurogenesis in the human hippocampus has generally been recognized and accepted (Eriksson et al., 1998), the incidence of olfactory neurogenesis in the human brain has been an ongoing subject of debate (Kirschenbaum et al., 1999; Pagano et al., 2000; Curtis et al., 2007; Sanai et al., 2011; Ernst et al., 2014). A recent report by the Mechawar group provided evidence for the occurrence of doublecortin (DCX) positive neuroblasts in the SVZ-OB path in the post-mortem brains from suicide subjects (Maheu et al., 2015). However, the evidence for the migration of neuroblasts and mechanisms underlying their migration towards the OB in the normal human brain are yet to be validated. In non-primate mammalian brains, the glial tube structure of the RMS provides a scaffold platform for the migrating neuroblasts towards the OB (Lois and Alvarez-Buylla, 1994; Doetsch et al., 1999; Ming and Song, 2011). A reciprocal interaction between the neuroblasts and glial cells through the assistance of cell surface adhesion molecules, extracellular matrix, metalloproteases, transcription factors, neurotransmitters, neurotrophins and chemo-attractants have been suggested to mediate this distinct long-distance cell migratory process in the adult forebrain (Gritti et al., 2002; Ghoshghaei et al., 2007; Ming and Song, 2011). Besides the glial tube, directional flow of the cerebrospinal fluid (CSF) mediated by the ciliary movement of ependymal cells in the ventricle has been proposed to play a critical role in the migration of neuroblasts along the SVZ—RMS-OB path (Sawamoto et al., 2006). For yet unknown reasons, the RMS structure in the human brain seems to be restricted to the developmental stage and absent in the adulthood (Kam et al., 2009; Sanai et al., 2011; Wang et al., 2011).
was found to be reduced in the SVZ of late stage tgHD rats (Kandasamy et al., 2015). Moreover, the reduced NSC proliferative capacity in the SVZ appeared to be compensated by the enhanced mitotic events of neuroblasts in late stage transgenic HD rats (Kandasamy et al., 2015). This might be also the case in the SVZ of other genetic models of HD with different grades of behavioral and neuropathological symptoms (Kandasamy et al., 2011; Velusamy et al., 2017). As a result, a vigorous migratory pattern of neuroblasts, instigated towards the degenerated striatum was highly pronounced at the expense of olfactory neurogenesis in most genetic models, which in part, mimicked the reactive neurogenesis reported in the SVZ or SEL-striatal regions in the brains of the toxic QA-injected experimental rat model (Tattersfield et al., 2004) and human HD brains (Curtis et al., 2007; Ernst et al., 2014), respectively. Taken together, reactive neurogenesis resulting from the striatal migratory event of neuroblasts seems to be a unique cellular trait, signifying the emergence of regenerative foci in the striatum of HD brains throughout the animal kingdom including humans. This abnormal proliferation of neuroblasts in the SVZ and their migration into the vulnerable striatum have recently been recognized as “reactive neuroblastosis” in the tgHD rat model (Kandasamy et al., 2015; Velusamy et al., 2017). Apparently, in this context, the process of neurogenesis is prematurely terminated, i.e., the cell die before they mature and before they integrate into the striatal circuitry (Figure 1). In the human HD brain, the situation seems to be similar (Ernst et al., 2014). Interestingly, the phenomenon of reactive neuroblastosis seems not to be restricted to HD pathology, but has recently been reported also in brains of ALS patients associated with dementia (Galán et al., 2017). Taken together, the proposed reactive neuroblastosis event observed in the striatum of the adult brain requires a great scientific consideration as it provides a fresh perspective on neurobiology of aging and disease, epitomizing a potential therapeutic target for in vivo forebrain regeneration. Hence, the functional relevance of reactive neuroblastosis and its consequence should be carefully considered in progressive neurodegenerative disorders. Likewise, where appropriate, the reactive neuroblastosis process needs to be investigated in acute neurological complications such as stroke, seizure, neuroinflammatory disorders and traumatic brain injuries.

**TGF BETA SIGNALING AND HUNTINGTIN PROTEIN AS POTENTIAL MEDIATOR OF CELLULAR EVENTS**

As mentioned above, SVZ-striatal neurogenesis in HD is characterized by reduced stem cell activity, reactive neuroblastosis and by premature death of the young neurons. An essential question is of course the physiological and molecular regulation of these events. We are postulating a framework that integrates physical activity, transforming growth factor-beta and mutant huntingtin protein as potential regulators. Physical exercise has been unequivocally shown to prevent cognitive decline by facilitating neurogenesis specifically in the hippocampus of healthy adult brains (van Praag et al., 1999). However, physical exercise has failed to ameliorate impaired hippocampal neurogenesis in the R6/2 (Kohl et al., 2007) and N171-82Q (Potter et al., 2010) models of HD. Also, physical exercise failed to influence the SVZ derived OB neurogenesis in the healthy brain (Brown et al., 2003). Therefore, hippocampal and SVZ/OB neurogenesis are differentially affected by regulatory signaling mechanisms, and physical activity is not counteracting the impaired hippocampal neurogenesis observed in HD animal models. Interestingly, a routine physical exercise practice has accelerated pathogenesis in a marathon runner who had been diagnosed with pre-symptomatic HD (Kosinski et al., 2007). The reason for this is unclear, but signaling mediated by TGF-beta might be crucially involved. First, physical exercise has been shown to induce the expression of TGF-beta in the normal healthy brain and to suppress spontaneous motor activity (Inoue et al., 1999). Second, physiological levels of TGF-beta and its downstream signaling pathway have been linked to the regulation of NSC’s self-renewal, migration, integration and survival of neuroblasts in the normal adult brain (Kandasamy et al., 2014), and experimentally elevated levels of TGF beta in the adult brains hindered the proliferative potential of NSCs and neurogenesis in the hippocampus (Buckwalter et al., 2006; Wachs et al., 2006; Aigner and Bogdahn, 2008). Similarly, analysis of phosphorylation events of Smad2, a downstream component of TGF-beta signaling in the hippocampal stem cell niches of R6/2 mice and tgHD rats, revealed that elevated levels of TGF beta/Smad2 signaling play a crucial role in the induction of quiescence of NSCs leading to reduced hippocampal neurogenesis (Kandasamy et al., 2010). Third, an increased Smad2 phosphorylation observed in the ectopically migrating neuroblasts from the SVZ towards the striatum of HD brain indicated a possible role of TGF-beta signaling in the migration/early differentiation of neuroblasts (Kandasamy et al., 2015; Figure 1). In the healthy brain, this might well promote structural and functional differentiation and maturation of neurons, however, in the HD brain, this might be completely different: although very speculative, involuntary hyperkinetic movements (Chorea) might cause increased levels of TGF-beta in the HD brains. In consequence, as Bowles et al. (2017) had shown, this might lead to the upregulation of mutant huntingtin protein through the activation of Smad3, a binding partner of Smad2, and the increased mutant huntingtin protein levels might trigger the apoptotic events in SVZ derived neuroblasts or young immature neurons (de Luca et al., 1996; Schuster and Krieglstein, 2002). In summary, the elevated levels of TGF-beta in the HD brain might on one hand cause a lower level of NSC activity, and through elevation of mutant huntingtin expression cause a premature death of differentiating neuroblasts regardless of the origin of the neuroblasts. For example (Magnusson et al., 2014) demonstrated that a subset of astrocytes have the capacity to produce new neurons in the striatum independent of the SVZ, while a striatal specific stem cell niche is yet to be recognized (Magnusson et al., 2014). Also here, elevated TGF-beta levels might finally reduce the levels of neuronal production and the survival of the new neurons. Taken together, it can be proposed that therapeutic physical
exercise and/or hyperkinetic movements in HD subjects might play a major role in impeding adult neurogenesis through elevated TGF-beta/Smad2 signaling, which might elevate the expression of mutant huntingtin protein in neuroblasts leading to premature death of these cells. In contrast, in the healthy brain, physical exercise induced TGF-beta/Smad signaling may act in synergy with huntingtin protein, and this in turn can lead to terminal differentiation of neuroblasts resulting in functional neurogenesis. The source of the elevated TGF-beta levels upon physical exercise in the healthy brain is not known, under pathological situations, activated microglia and reactive astrocytes are potential sources of TGF-beta (Lindholm et al., 1992; Doyle et al., 2010; Kandasamy et al., 2010).
IMMUNOLOGICAL AND NON-NEUROGENIC ROLES OF REACTIVE NEUROBLASTOSIS IN THE ADULT STRIATUM

Reactive neuroblasts in the HD brains might be immunologically active and modulate microglia activities. Microglia have been strongly implicated in immune surveillance and synaptic pruning (Kettenmann et al., 2013), and they are responsible for synaptic integration of new-born neurons, thereby supporting the neuroplasticity of adult neurogenesis (Ekdahl, 2012). A substantial number of reports suggested that disruption of microglial functions along aging and neurodegenerative processes leads to synaptic dysfunctions, neuronal loss and, consequently, to cognitive impairments (Morris et al., 2013). The activated microglia mediated prolonged neuroinflammatory responses have been well recognized in HD (Sapp et al., 2001; Crottì et al., 2014).

In an independent attempt to characterize microglial cells in the HD brain using ionized calcium binding adaptor molecule 1 (IBA 1) staining, the SVZ-region of early stage tgHD rats showed an indication for microglial activation compared to controls. In contrast, a drastic reduction in the number of microglial cells was observed in parallel with the invasion of neuroblasts in the striatum of late stage tgHD rats compared to the early stage and that of age matched controls (unpublished own data). One possible reason might be a non-cell autonomous mechanism, by which the glial specific expression of mutant huntingtin protein can induce prolonged reactive astrocytosis and activated microgliosis (Bradford et al., 2010; Ehrlich, 2012). Abnormal glial cell activity may result in depletion of microglia and astrocytes due to phagocytosis in the pathogenic HD brains. Thus, the observed reactive neuroblasts in the SVZ deviating towards the striatum may also be an immunological response in order to compensate for the reduction in glial cells, particularly the depletion of microglia in late stage of HD.

Previously, Kohl et al. (2010), demonstrated that the expression of the mutant huntingtin protein was specifically found in the dopamine- and cAMP-regulated neuronal phosphoprotein (DARPP)-32 positive cells of the inner striatum of R6-2 mice. However, the expression of the mutant huntingtin protein appears to be delayed in the proliferating precursor cells of the striatum adjacent to the SVZ in R6/2 animals (Kohl et al., 2010). This observation closely overlaps and corresponds to the process of reactive neuroblastosis, in which, the absence of mutant huntingtin protein and pSmad2 in the neuroblasts has been proposed for the delayed terminal differentiation of new neurons in the adjacent striatum of HD subjects (Kandasamy et al., 2015).

Besides an immunomodulatory role, a concomitant experimental evidence using transcriptome analysis of NSCs suggested that induced levels of TGF beta can suppress the expression of Myelin basic protein (MBP), a marker of oligodendrocytes (Kandasamy et al., 2014). While conditional expression of the mutant huntingtin protein has been shown to induce apoptosis in oligodendrocytes, demyelination can be expected in the striatum of HD subjects (Huang et al., 2015). Thus, impaired myelination process in the striatum, in part, might be responsible for the failure in the synaptic plasticity of newly generated neurons (Alizadeh et al., 2015; Bourbon-Teles et al., 2017). Taken together, it can be postulated that the selective proliferation of neuroblasts responsible for reactive neuroblastosis may partly take over neuroinflammatory functions of glial cells in the absence or dysfunction of microglia or astrocytes in the HD striatum. Besides, depletion or dysregulation of neurotransmitter inputs have been shown to induce the migration of neuroblasts towards the striatum by compromising the cell proliferation in the SVZ (Winner et al., 2006). Thus, the migrating neuroblasts might also provide an alternate source of neurotransmitters, trophic and growth factors involved in synaptic plasticity to support the function of the striatum. It certainly demands further experiments to investigate the additional roles of neuroblastosis with respects to immune defense, trophic support and synaptic pruning compared to glial cells in the adult brain. Thereby, the extra-neurogenic roles of normal and reactive neuroblasts can functionally be addressed for many acute forms of neurological diseases such as stroke and epileptic seizure.

THE FUNCTIONAL ROLES OF NEUROBLASTS IN THE STRIATUM OF THE ADULT BRAIN

A significant scientific progress has been made in understanding the physiological roles and regulation of adult neurogenesis in aging and disease (Deng et al., 2010; Couillard-Despres et al., 2011; Marschallinger et al., 2015). The generation and functional integration of the new born neurons in the adult brain enticed by physical activity (van Praag et al., 1999; Vivar et al., 2013) and environmental stimuli (Kempermann et al., 1997; Zhao et al., 2008; Ming and Song, 2011) not only contribute to neural plasticity but also facilitate brain regeneration and functional recovery upon acute brain injuries and progressive neurodegenerative conditions (Nakaguchi et al., 2011). The primary roles of hippocampal neurogenesis have been demonstrated to be linked with pattern separation, mood regulation, contextual learning and memory processes (Clelland et al., 2009), whereas the SVZ derived neurogenesis in the OB has been implicated in odor discrimination and sexual desire (Sakamoto et al., 2011; Feierstein, 2012; Hill et al., 2015). Interestingly, evidence for the occurrence of adult neurogenesis has also been established in amygdala (Jhaveri et al., 2017), hypothalamus (Paul et al., 2017) and cortex (Gould et al., 1999) responsible for fear memory, HPA-axis and motor control, respectively. Thus, different brain regions sustain the regenerative potential to establish new neurons in the adult stage.

The striatum is a central part of the basal ganglia, responsible for the functionality of limbic system attributed to voluntary motor control, reward process, cognitive functions and behavior.
POSSIBLE LIMITING FACTORS OF THE ANALYSIS OF NEUROBLASTS IN THE ADULT BRAIN

Obviously, there are still limitations in the techniques that are used to detect and to analyze neurogenesis. Recently, Jonas Frisén and colleagues have implemented the radioactive carbon dating procedure to estimate the persistence of neurogenic process in the striatum and RMS-OB path along the aging process and in HD human brains (Bergmann et al., 2012; Ernst et al., 2014). Though there was no traceable amount of neuroblasts observed in the RMS, turnover of an interneuronal population in the striatum was evident in adult human brains (Ernst et al., 2014). The striatal turnover of neuroblasts is likely to be originated in the SVZ, but the survival of neuroblasts was found to be diminished in the striatum of both the healthy and HD human subjects (Ernst et al., 2014). Eventually, the disoriented neuroblasts originated from the SVZ failed to differentiate, integrate and survive in the human striatum (Ernst et al., 2014), confirming the previous reports on R6/2 mouse (Kohl et al., 2010) and tgHD rat -models of HD (Kandasamy et al., 2015). Interestingly, validation of neurogenesis in the RMS-OB path using radioactive 14C dating enforced the view that the human OB is devoid of ongoing neurogenesis in the adulthood (Wang et al., 2011; Bergmann et al., 2012). This is somewhat contradictory to a previous report in which (Curtis et al., 2007) using BrdU labeling method demonstrated that the migration of neuroblasts through the RMS contributes to neurogenesis in the OB of the human brain. Both paradigms for tracing newly divided cells in the human brain, either using nucleotide analogs or radioactive 14C, have their own merits and limitations. For example, it has generally been believed that intake of food represents the primary source of carbon in the human body. However, the olfactory epithelium of the nasal mucosa is connected with the OB through the fila olfactoria, in which a fraction of atmospheric air and volatile pheromones are able to reach the OB during respiration (Coates, 2001; Lahir and Forster, 2003; Sun et al., 2009; Gao et al., 2010). As reported earlier, the OB can sense the atmospheric CO2 (Hu et al., 2007; Gao et al., 2010; Carlson et al., 2013) where it can diffuse into bio-available metabolites in the brain through a CO2 fixation process (Berl et al., 1962; Pincus, 1969; Lahir and Forster, 2003; Scott, 2011). Thus, a considerable amount of radioactive 14C depletion can be expected specifically in the genome of mitotically active cells in the human OB due to the well-known “Suess effect” (Stenström et al., 2010; Graven, 2015; Lång et al., 2016), through which radioactive 14C can be exchanged by normal 12C from the atmospheric CO2 and some organic volatile compounds such as pheromones (Pinto, 2011; Cazakoff et al., 2014; Ajmani et al., 2016). Moreover, the radioactive 14C decay has been considered a spontaneous and highly random process, as different 14C atoms can radically be reverted into 14N atoms at different degrees due to a subatomic transmutation process. The safety guideline and dosimetry of radioactive elements suggest that 14C is a low energy beta emitter and therefore a short-term external exposure may be
discharged from a large quantity of radiation (Pauling, 1958). In turn, a magnitude of radiation incorporated cells in close proximity might intensify the dose of intrinsic emission of harmless (Pauling, 1958; Kim et al., 2010). However, according to Pauling, it would also be expected that a prolonged cell intrinsic emission of $^{14}$C radiation and accumulation of $^{14}$C incorporated cells in close proximity might intensify the dose of radiation (Pauling, 1958). Hence, radioactive $^{14}$C based tracing of neurogenesis in the human brain may require further validation to include, if present, any false negative results or artifacts. Similarly, the incorporation of halogenated thymidine analogs by apoptotic cells (Cooper-Kuhn and Kuhn, 2002), their toxic effects on cell viability (Lehner et al., 2011), DNA instability or repair mechanisms and phagocytosis events rendered by microglia also require a careful consideration (Rakic, 2002). Nevertheless, it has widely been accepted that neurogenesis occurs in adult brain as it provides a foundation for neural plasticity across the animal kingdom (Ming and Song, 2011; Velusamy et al., 2017). While multiple intrinsic and extrinsic stimuli have been shown to regulate adult neurogenesis in the hippocampus and the SVZ-OB, its regulation in the striatum has become an important topic of elucidation.

CONCLUSION

The naturally occurring stem cell mediated neuroregenerative processes in the adult brain under physiological condition provides a clue in ascertaining a potential therapeutic target for many neurodegenerative disorders including HD. The occurrence of SVZ derived neuroblasts as a part of neurogenic processes in the adult brain under physiological condition provides a clue in ascertaining a potential therapeutic target for many neurodegenerative disorders including HD. Therefore, investigation into the molecular mechanism involved in reactive neuroblastosis at the levels of cell proliferation, migration, integration and survival in the damaged area may provide a clue for therapeutic intervention not only for treating HD but also for a variety of neurological deficits such as stroke, Parkinson’s disease and Alzheimer’s disease.

AUTHOR CONTRIBUTIONS

MK: manuscript preparation and writing, preparation of figure.
LA: manuscript preparation and writing.

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