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Review

The growth factors cascade and the dendrito-/synapto-genesis versus cell survival in adult hippocampal neurogenesis: The chicken or the egg

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ABSTRACT

The decision between cellular survival and death is governed by a balance between proapoptotic versus antiapoptotic signaling cascades. Growth factors are key actors, playing two main roles both at developmental and adult stages: a supporting antiapoptotic role through diverse actions converging in the mitochondria, and a promoter role of cell maturation and plasticity through dendritogenesis and synaptogenesis, especially relevant for the adult hippocampal neurogenesis, a case of development during adulthood. Here, both parallel roles mutually feed forward each other (the success in avoiding apoptosis lets the cell to grow and differentiate, which in turn lets the cell to reach new targets and form new synapses accessing new sources of growth factors to support cell survival) in a circular cause and consequence, or a "the chicken or the egg" dilemma. While identifying the first case of this dilemma makes no sense, one possible outcome might have biological relevance: the decision between survival and death in the adult hippocampal neurogenesis is mainly concentrated at a specific time window, and recent data suggest some divergences between the survival and the maturational promoter effect of growth factors. This review summarizes these evidences suggesting how growth factors might contribute to the live-or-die decision of adult-born immature granule neurons through influencing the maturation of the young neuron by means of its connectivity into a mature functional circuit.

1. Cell survival and apoptosis during development, adult life and a case of development during adult life

The decision on living or dying is a delicate balance between proapoptotic and antiapoptotic signals the neural cell may have to take throughout its entire lifespan, especially whether the cell's homeostasis becomes impaired after insults, lesions, by neurodegenerative diseases, or the panoply of well-known instances where the apoptotic machinery is triggered. This balance is maintained for all cells throughout the lifespan of the individual (for a review, see for example Benn and Woolf, 2004). The purpose and the characteristics of this balance show relevant similarities and differences between development and adult. During development, this decision is taken as a function of the general process of building a genetically programmed neural circuit, by means of the production of a higher number of cells than the number really needed, and the ongoing death of the spare neurons. The critical element is the limited availability of growth factors (in the present work, we will distinguish between specific growth factors when required; otherwise we will refer to growth factors in a generic way, indicating that the mentioned action is valid for several growth factors; we have focused this work mainly on BDNF and IGF1). The *by default* mechanism is the physiological programmed cell death. Only the neurons able to get access to enough amounts of released growth factors will brake the onset of the *by default* apoptosis. The rest of the cells will die. It makes sense that the fundamental source for these growth factors is the synapse, in order to build adequately the scheduled circuit. On the contrary, during adult life this decision seems to be no longer needed on a normal physiological basis, as the neural circuit is already fully formed and functional; rather the circuit needs to be actively maintained than trimmed, therefore the apoptotic machinery is switched off, and the growth factors are no longer required for this purpose (see below about the roles of growth factors during adulthood). The reasons why the decision might have to be taken during adult life are the threats compromising the homeostasis of the cell, as several stressors, excitotoxicity, reactive oxygen species and other insults, as well as metabolic impairments caused by diseases, can accumulate along the lifespan. Whether these insults are balanced with the antiapoptotic factors the cell contains for buffering the damage,

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the cell will stay alive; whether the insults exceed the supporting ability of the antiapoptotic factors, the apoptotic machinery will switch on pathologically. Nevertheless, both the proapoptotic and the antiapoptotic factors operate by means of essentially the same mechanisms during development and adult life (Kim and Sun, 2011; Kuranaga, 2012; Hyman and Yuan, 2012). Briefly, the common executive pathway of apoptosis is mediated by effector caspases 3 and 7. These caspases are activated either by JNK or by the cytochrome C-induced apoptosome, and the growth factors counterbalance the activation of these cascades by inhibiting the JNK pathway and/or promoting preferential allocation of BAX in the cytosolic compartment (against mitochondrial compartment) by the reduction of BH3 protein expression-induced activation of BCL-2 and the activation of other antiapoptotic genes. This allocation of BAX impedes cytochrome C release from mitochondria to cytosol where it would induce the final apoptotic cascade (Deckwerth et al., 1996; Li et al., 2001; Putcha et al., 2002; Putcha and Johnson, 2004; Benn and Woolf, 2004). As this delicate balance is at the core of the developmental programs, as well as of the homeostatic maintenance of both the pathological and normal adult nervous tissue, the knowledge about the factors and mechanisms governing this decision are crucial for our understanding of the proper functioning of the neural system.

In this work, we will consider pro-survival actions as those giving trophic support to a cell, mainly mediated by direct effects on the mitochondria or through the regulation of antiapoptotic genes as described above, while a net effect on dendrite elongation or branching, spine outgrowth or synapse formation are considered as specific actions driven by a direct, local influence. It is important to note that both the actions on the mitochondrial function and the antiapoptotic genes take place concomitantly with the effects on neurite branching, spine formation and synapse formation and consolidation. It is usually stated that both roles are temporally indistinguishable for three reasons: first, because the survival of the cell leads to its growth, maturation and differentiation, that in turn means the neurites are branching, contacting with either input signals or output targets, and gaining access to more growth factors or neurotrophins that again maintain the cell homeostasis and leads to survival. Second, because most growth factors play both roles. Third, because some degree of promiscuity exists in the mechanisms mediating both processes, specially accounting for caspases (Hyman and Yuan, 2012). This cause and consequence loop is an endless process throughout development. During adulthood, the circuits are maintained as a function of its intermittent activity, in this case by promoting dendrite branching, the contact with the input signals and formation of spines and synapses. The access to growth factors is again a key factor to consolidate the circuit and maintain the connectivity. But in this latter case, the final result is to achieve neural plasticity, not necessarily the cell survival. However, some discrete regions exist in adult brain where a bulk of new neurons is formed to be integrated in mature circuits, about which we will next discuss.

One of the most challenging events for the elucidation of the mechanisms governing the live-or-die decision of neurons is the case of ongoing "developmental" processes into the adult brain: adult neurogenesis. It is well known that many of the mechanisms working in the developmental formation of the hippocampal dentate gyrus are also working during adult neurogenesis of granule neurons (Esposito et al., 2005), including programmed cell death mechanisms, although some interesting differences have been revealed (Kim and Sun, 2011). However, in the case of adult hippocampal neurogenesis, there is not a globally orchestrated process to build all circuits at the same time in an orderly manner; the circuits are already mature and functional, and the new connections established by the newborn neurons have to be aligned with the old ones not only without disturbing them but besides contributing to the proper functioning of the system, as a huge number of evidences suggests the adult hippocampal neurogenesis (AHN) displays relevant, distinct functions in the adult dentate gyrus (Kempermann, 2011). AHN takes place from neural precursors located at the dentate subgranular zone, whose progeny are actively dividing progenitors (Alvarez-Buylla et al., 2001; Gil-Perotin et al., 2009; Seri et al., 2001). These progenitors form postmitotic immature neurons which grow and mature into the granule cell layer (Kempermann et al., 2003). Their axons grow to finally make contacts mainly with the dendritic arbor of CA3 neurons (Hastings and Gould, 1999; Markakis and Gage, 1999; Stanfield and Trice, 1988; Zhao et al., 2006), while the dendrites grow beyond the granule cell layer into the molecular layer to make most of their contacts with the perforant axons from entorhinal projection neurons (Zhao et al., 2006). The "developmental" schedule of these newborn immature neurons is still under investigation but many data has been already accumulated (Esposito et al., 2005; Kempermann, 2011). It is especially relevant for the main message of this work the existence of a critical period for the development of the newborn granule neurons around days 12–15 after cell birth (when the first spines are formed at the distal dendritic branches (van Praag et al., 2002; Tashiro et al., 2006; reviewed by Bergami and Berninger, 2012)), followed by a crucial time window lasting along the third and fourth weeks after cell birth (Bruel-Jungerman et al., 2006; Ge et al., 2007; Kee et al., 2007; Tashiro et al., 2007), when the cell either becomes finally integrated into the circuit or dies (Kempermann, 2011). Around day 12 after cell birth, the growing axon reaches the dendrites of CA3 region. Few days later, the dendrites of the new cells begin to form spines (Zhao et al., 2006). This is a critical time period, during which the cell needs to make contacts with the perforant entorhinal axons. Failing this process will lead to apoptosis. This apoptosis takes place after 3–4 weeks after cell birth. Between both events, there appears to be a time period critical for the survival-or-die decision. The relevant point is that this specific timing is paralleled by the mentioned growth to a specific subarea of the molecular layer where entorhinal axons are waiting for the growing granule dendrites. Although the growth and maturation of the axons is also highly timed and coordinated with the dendritic shaft, the precise sequence of the morphological changes taking place at dendrites matches with the time the cell has to survive or die (see below the comparison of the effects of BDNF signaling removal between dendrites and axons, in Section 5).

What is the criterion to select the new neurons in adult hippocampal neurogenesis? These neurons have two main fates: to mature into new granule neurons, fully indistinguishable from postnatal-generated granule neurons, displaying essentially the same electrophysiological properties, but also, to play distinct, relevant roles while still being immature, as recent, accumulating evidences points out (Deng et al., 2010; Aimone et al., 2011). Concomitantly, a necessary property related to these putative specific roles is that this subpopulation of immature granule neurons is specifically regulated both by physical activity and enrichment (Llorens-Martin et al., 2010, 2011). But in the process of maturing from differentiating immature neurons to fully mature granule neurons, a higher number of immature neurons are generated than the number finally needed, as in development. The factor determining the number of neurons required by the system is the degree of activity of the organism, both physical and cognitive activity. Both kind of activities are interrelated (Aberg et al., 2006; Llorens-Martin et al., 2009), and contribute to define the neural resources necessary to manage the information burden to be processed (although a recent work also suggests that the processed information burden and the hippocampal neurogenesis rate might be influencing each other along the juvenile to adult stages transition (Freund et al., 2013), in a process possibly influenced by an epigenetic regulation, active and ongoing from prenatal development to adulthood).