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Review

Naturally occurring neuronal death during the postnatal development of Purkinje cells and their precerebellar afferent projections

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Abstract

Naturally occurring neuronal death plays a substantial developmental role in the building of the neural circuitries. The neuronal death caused by different cerebellar mutations is mostly of an apoptotic nature. Apart from the identity of the intrinsic mechanisms of the mutations, adult cerebellar mutants are a powerful tool to causally study the development of the cerebellar connectivity. Thus, studies on adult cerebellar neuronal cell death occurring in mouse mutants elucidate: (i) the dependence of the postsynaptic neurons on their partners, (ii) the 'en cascade' postsynaptic transneuronal degeneration after target-deprivation, and (iii) the close relationship between the molecular modular organization of the cerebellar cortex and dying Purkinje cells. Neuronal cell death has been extensively studied in developing olivocerebellar system. However, less data are available on the occurrence of naturally occurring neuronal death during the in vivo normal development of the Purkinje cells and the mossy fiber system neurons. The developmental role of neuronal death during the establishment and refinement of the olivocerebellar projection is currently discussed. Moreover, the occurrence of neuronal death during the development of the basilar pontine nuclei and its role in the acquisition of the adult pontocerebellar projection is still poorly understood. In the present review, we correlate the dates of Purkinje cells death with the inferior olivary and basilar pontine neuronal apoptosis, discussing their developmental relationships during the elaboration of the fine-grained maps of the cerebellar afferent connections.

Theme: Development and regeneration
Topic: Neuronal death

Keywords: Basilar pontine nuclei; Cerebellar cortex; Climbing fiber; Mossy fiber; Inferior olive; Naturally occurring cell death; Purkinje cell; Topographic map of connection

Contents

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1. Introduction

Naturally occurring cell death plays a crucial role in the development and homeostasis of pluricellular organisms. Since the pioneering analysis of Hamburger [50], naturally occurring neuronal cell death (NCD) has been correlated with the control of neuronal cell number during development (for a review, see Ref. [87]). NCD is involved in the withdrawal of aberrant axon projection or cell positions, the target-dependent matching of the sizes of both pre- and postsynaptic populations, and the refinement of the neural circuits [24,34,93]. These regressive phenomena depend of the competition between neurons for the trophic factors required for survival [22,87,94]. The decrease in or absence of appropriate trophic factors triggers an intrinsic genetic program—requiring specific protein synthesis [88]—which leads to cell death [87].

NCD is determined by the balance between the expressions of pro- and anti-apoptotic genes (for a review, see Refs. [65,79,87]). The breakdown of this balance elicits the activation of the caspases protein family [84] whose action results in DNA fragmentation and the formation of the apoptotic cell bodies. Among the caspases family members participating in programmed cell death, caspase-3 is the most frequently involved in the apoptosis of postmitotic neurons [92,100,121]. Caspase-3-independent apoptosis [125] and a neuroprotective role for caspase-3 against *N*-methyl-D-aspartate neurotoxicity [78] have also been recently suggested. Active caspase-3 immunocytochemistry is, however, a useful tool to detect neurons undergoing apoptosis during the nervous system development [47].

NCD occurs during the development of Purkinje cells (PCs) [47,64] and their main primary afferents: the granule cells [60,118] and the inferior olive (IO) neurons [12,37]. The relationships of cerebellar and precerebellar NCD with: (i) the final organization of the highly precise pattern of adult cerebellar circuitry [6,35,46,56], and (ii) the intrinsic cerebellar cortex molecular compartmentation, have been largely discussed [72,103]. Moreover, the absence of NCD during the development of the basilar pontine nuclei (BPN) [8]—an important mossy fiber cerebellar afferent system—is an exception to the general observation of regressive phenomena taking place during nervous system development, in which NCD plays a key role in the refinement of neural circuitries [88].

This review explores the temporal relationships between NCD in PCs and in two major afferent sources—the IO and the BPN. Evidence is presented that NCD occurs in the BPN concurrently with the refinement of the adult cerebellar topography.

2. Purkinje cell death

Since the elegant description of Ramón y Cajal [96], it has been clear that PCs are the output of the cerebellar cortex, and receive extra-cortical inputs directly from the IO via the climbing fiber system, and indirectly, relayed through the parallel fibers of the granule cells, from the rest of the cerebellar afferents (for a review, see Ref. [127]). PCs are generated in the ventricular zone of the cerebellar primordium [2,80]. Newborn PCs migrate to the cerebellar plate following specific cadherin parasagittal guides [72], where they aggregate in a layer 6–10 cells thick which, during the early postnatal period, evolves in a monolayer lying between the molecular and the granular layers of the cerebellar cortex. PCs have been proposed as the main organizer of the cerebellar cortex and its afferents [9,113], by regulating the proliferation rate of the external granular layer [111], and providing a map of molecular cues that defines the organization of the cerebellar afferent topography [28,29,113,132]. The molecular heterogeneity of PCs is present from embryonic life to adulthood. PCs present a mediolateral pattern defined by the differential expression of regulatory genes (i.e., *En-2*, *En-1*, *Wnt-7B*, and *Pax-2*) [68,111], morphogenetic factors (i.e., ephrins and Eph receptors) [62,111], and cell adhesion molecules [28,72]. Heterogeneity is also evidenced by the patchy asynchronous expression of several markers of adult PCs (i.e., guanosine3′:5′-phosphate-dependent PK and calbindin) [128,129]. During early postnatal life, the expression of these markers becomes uniform for all PCs, and the modular design of the cerebellar cortex is now defined by the expression of adult PC biochemical markers that delineate the definitive adult parasagittal compartmentation of the adult cerebellum (i.e., zebrin II; for a review, see Ref. [54]).

Young postmigratory PCs pass through four stages before the building of their definitive dendritic trees: (i) simple-fusiform cell, (ii) complex-fusiform cell, (iii) PC with regressive-atrophic dendrites, and (iv) stellate cell stage [5]. The analysis of these early stages demonstrated that PC maturation is also asynchronous during the first 5–6 days of postnatal life. Thus, adjacent PCs in different stages of dendritogenesis are found within the same region of the same cerebellar folia (see Fig. 1 in Ref. [5]). Whether asynchronous PCs belong to the same developmental molecular cluster could not be established in these HRP in vitro analyses. However, evidence from immunocytochemical analyses suggests that PCs within a developing stripe are at a similar stage of dendritic development but different stripes may be at different stages (Hawkes, personal communication). The transition from simple to regressive-atrophic dendrites PC stage implies a process of active