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Cortical developmental death: selected to survive or fated to die

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The mature cerebral cortex only contains a fraction of the cells that are generated during embryonic development. Indeed some neuronal populations are produced in excess and later subjected to partial elimination whereas others are almost completely removed during the first two postnatal weeks in mice. Although the identity of cells that disappear, the time course and mechanisms of their death are becoming reasonably well established, the meaning of producing supernumerary cells still remains elusive. In this review, we focus on recent data that shed a new light on the mechanisms involved in adjusting cell numbers and discuss the significance of refinement versus complete elimination of cell populations in the developing cortex.

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Introduction

Programmed cell death (PCD) is a biological process which serves crucial functions in the body. It is used to match numbers of distinct cell types in tissue homeostasis, to remove aberrant cells, to eliminate transient structures or to shape organ morphogenesis [1]. In the nervous system PCD fine-tunes the density of neuronal populations and their targets. The so-called trophic theory states that neurons compete for target-derived survival factors available in limited amounts, leading to the elimination of up to 50% of neurons [2–5]. Although this theory is largely supported by experimental evidences in the peripheral nervous system, it remains to be demonstrated in the central nervous system (CNS) where survival has not been linked formally to growth factor(s). Furthermore, in the cerebral cortex several populations of cells exist that almost completely disappear during the first two postnatal weeks. This seems to be a unique characteristic of the mammalian neocortex not reported in other territories of the nervous system and used in different organs to fully eliminate embryonic or unwanted structures such as patterning centers or sex-specific primordia [1].

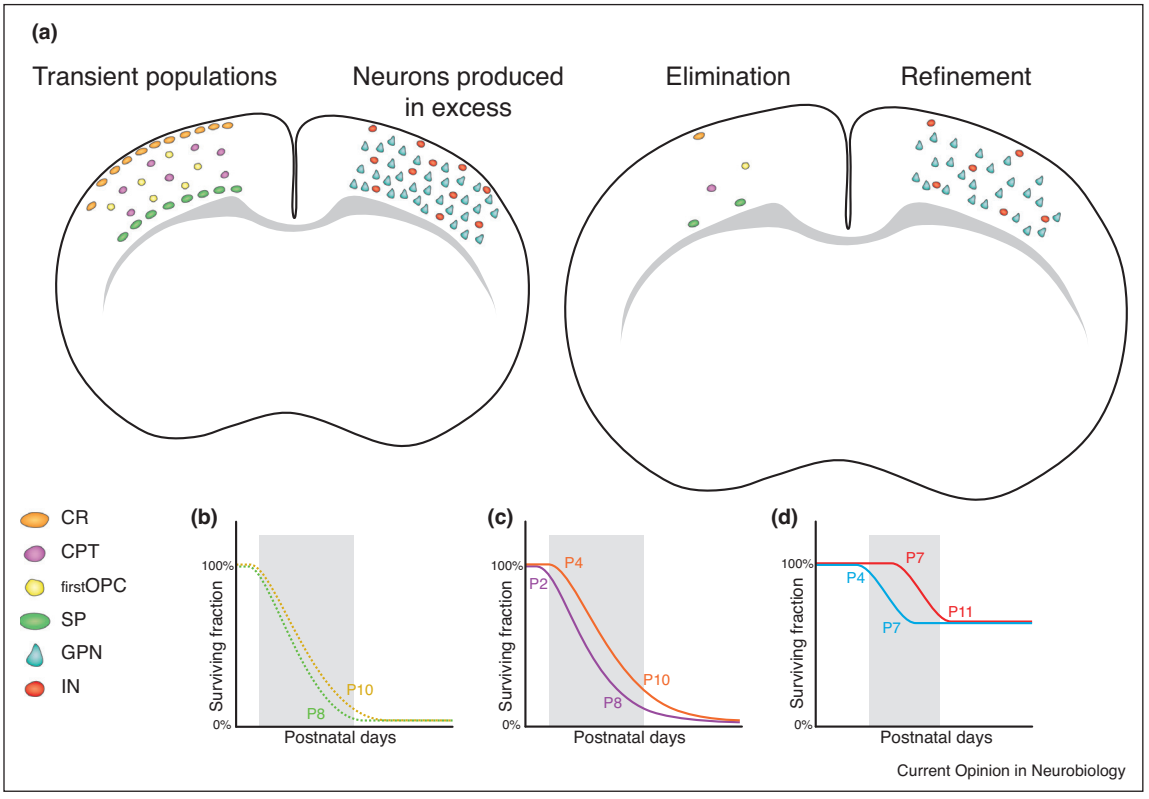
Processes of cell death in the developing nervous system have been extensively reviewed elsewhere [4–8]. Here we will especially focus on the cerebral cortex and survey recent data shedding light on cell populations either subjected to partial elimination or complete removal during development and discuss the potential relevance of their disappearance in the construction of functional and dysfunctional neural circuits.

Refinement of neuronal numbers versus complete removal in the developing cortex

In the cerebral cortex, the existence of exuberant neurons and projections and their role during development has been studied for many years. Notably, an increase in transient axonal and cell populations has been suggested to correlate with the complexification of cortical circuits in primates [9]. Although cellular processes like neurogenesis, migration, synaptogenesis or myelination are recognized building bricks for circuit formation, the role of transient cells and their PCD in the assembly of nascent cortical networks is still poorly understood. Both glutamatergic projection neurons and more recently GABAergic interneurons were shown to undergo significant cell death at early postnatal stages in mice, leading to the disappearance of 30–40% of both cell types [10•,11•] (Figure 1a,d and Table 1). In addition, four populations identified so far massively disappear at the end of cortical development: Cajal-Retzius neurons (CRs), subplate neurons (SPs), cortical plate transient neurons (CPTs) and the first wave of embryonic oligodendrocyte precursors ($_{first}$OPCs) [12•,13•,14,15•] (Figure 1a–c and Table 1).

Characterizing the lifespan of populations which disappear is not an easy task. Earlier works heavily relied on histological hallmarks of cell death — most notably pyknosis and DNA fragmentation — which did not allow assessing cell identity. Activated Caspase-3 immunodetection has also been used extensively but given the short interval between Caspase cleavage and phagocytosis by

Figure 1



Cell populations subjected to postnatal developmental death. **(a)** Cajal-Retzius cells (CRs, orange), cortical plate transient neurons (CPTs, purple), the first wave of oligodendrocyte precursors ($_{first}$OPCs, yellow) and subplate cells (SPs, green) are almost completely eliminated whereas cortical interneurons (INs, red) and glutamatergic projection neurons (GPNs, blue) are subjected to partial elimination. **(b)–(d)** Extrapolated temporal windows of cell death and dynamics of disappearance of these populations are indicated with the same color code. Subtle differences might exist between populations, however they all undergo cell death within the first two postnatal weeks. Dashed lines for SPs and $_{first}$OPCs indicate the absence of precise time course.

macrophages (estimated to a few hours [16]) it is suitable only for studying populations which are either very large or that die synchronously over a short period of time. In addition, one should keep in mind the emerging roles of Caspase activation beyond apoptosis as well as Caspase-3 independent cell death [17–19]. On the contrary, lineage analysis in flies and nematodes, but also in mice thanks to genetic tracing, allows following cells throughout their life and unequivocally proving their absence or transformation during adulthood.

Mechanisms of refinement

It is well established that the neurotrophins NGF and NT-3 are required for the survival of most peripheral neurons. In the CNS, BDNF, which is the most expressed neurotrophin, does not display the same activity [5,20]. A very appealing explanation came with the discovery that both receptors for NGF and NT-3, TrkA and TrkC, but not the BDNF receptor TrkB, behave as 'dependence receptors', triggering cell death unless bound to their respective ligands [21,22]. Other growth factors such as IGF-1 and TGF-b1 were proposed to regulate cortical neuronal survival since their loss results in increased cell death [23,24]. However, their precise contribution to the selective elimination of cortical interneurons and projection neurons remains to be assessed. Southwell *et al.* [10•] proposed that interneurons death is not mediated by competition for trophic factors but rather by an intrinsic program following the observation that upon heterochronic grafts, interneurons die according to their own birthdate and not that of their environment. Yet, our global understanding of developmental cell death in the cortex remains fragmentary, reflecting either the existence of multiple cell-type specific extracellular and intracellular pathways (reviewed by [8]) and/or the implication of alternative mechanisms that do not fit with the classical neurotrophic theory.

Synaptic transmission has long been suggested to play a key role in controlling the balance between cortical cell survival and elimination [5,7,25]. Accordingly, cortical cell death peaks during the first two postnatal weeks, coinciding with the emergence of chemical synapses (Figure 1b–d). Three elegant studies recently formally