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Review

Molecular control of brain size: Regulators of neural stem cell life, death and beyond

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ABSTRACT

The proper development of the brain and other organs depends on multiple parameters, including strictly controlled expansion of specific progenitor pools. The regulation of such expansion events includes enzymatic activities that govern the correct number of specific cells to be generated via an orchestrated control of cell proliferation, cell cycle exit, differentiation, cell death etc. Certain proteins in turn exert direct control of these enzymatic activities and thus progenitor pool expansion and organ size. The members of the Cip/Kip family (p21Cip1/p27Kip1/p57Kip2) are well-known regulators of cell cycle exit that interact with and inhibit the activity of cyclin–CDK complexes, whereas members of the p53/p63/p73 family are traditionally associated with regulation of cell death. It has however become clear that the roles for these proteins are not as clear-cut as initially thought. In this review, we discuss the roles for proteins of the Cip/Kip and p53/p63/p73 families in the regulation of cell cycle control, differentiation, and death of neural stem cells. We suggest that these proteins act as molecular interfaces, or "pilots", to assure the correct assembly of protein complexes with enzymatic activities at the right place at the right time, thereby regulating essential decisions in multiple cellular events.

Contents

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Introduction

Proper organ development is dependent on a wide variety of parameters, including environmental inputs such as secreted signaling factors, cell–cell contact mediators, extracellular matrix, oxygen levels, gravity, nutrition, as well as intrinsic cues such as signaling pathways, transcription factor expression, DNA occupancy, and chromatin structure. A crucial component in regulating organ size is the balanced regulation of proliferation and cell death that is required to achieve the correct number of specific cell types within an organ and regions thereof. Whereas cells in many organs retain the capacity to divide also in the adult, other systems, such as the adult brain, consist to a large extent of non-dividing, postmitotic cells. Hence the delicate control of cell division, cell survival, cell cycle exit, and timing of differentiation during development is of utter importance to achieve the appropriate number of specific cell types, and the final size of the brain.

Most dividing cells in the developing brain are not fully differentiated and, at least during early and mid-gestation, to a large extent multi- or bi-potent. As they divide either symmetrically or asymmetrically, these progenitors will give rise to a continuous supply of undifferentiated progenitors by self-renewal [1]. In combination with the differentiation capacity, these progenitors are therefore often referred to as neural stem cells (NSCs). The progenitors and NSCs mostly reside in the ventricular regions of the developing brain. In the forebrain, including the developing cerebral cortex, these undifferentiated neural cells can be divided into apical and basal progenitors, where apical progenitors constitute the neuroepithelium and display NSC characteristics, whereas the basal progenitors reside in the subventricular zone and are often referred to as intermediate progenitors [1]. While being undifferentiated, these two classes of progenitors can be distinguished by several criteria, including differentiation potential and expression of markers such as specific transcription factors. Different regions of the central nervous system display variations in the principles of assembly. The development of the organization of the cerebral cortex is based on an "inside-out" manner where later-born neural progenitors migrate from the ventricular and subventricular zones past the earlier-born and thus settle in more superficial layers. In addition, interneurons (inhibitory) and populations of oligodendrocyte precursors migrate in a tangential manner from the ventral telencephalon to contribute to the cortical structures.

The right enzyme at the right place and the right time

In addition to the regulatory mechanisms underlying migration, axon pathfinding, and other fundamental principles underlying the rise of the exquisite architecture of the brain [2], proper cell division during brain development is depending on numerous precisely orchestrated events aiming at executing and coordinating spatially and temporally controlled enzymatic activities governing accurate DNA replication and chromatin modifications that should be inherited or erased to allow proper permission of gene activation and higher order chromatin structure. Control of multiple levels of micro- and nano-architectural subcellular organization is thus required to achieve the correct cellular phenotype. The correct guidance of enzymes, executed by transcriptional regulators, scaffold proteins, and nucleosome organization, in combination with the regulation of the activity of those enzymes that regulate acetylation, methylation, phosphorylation, ubiquitination, and additional modifications of the chromatin polymer and other structural components, is thus critical for multicellular existence.

In transcription, the cellular levels of certain enzymes influencing transcriptional activity, such as histone deacetylases and acetyl transferases, vary in a cell-specific fashion and display specific expression patterns during brain development and thereby provide cell-specific enzymatic activity [3]. Still, many of these factors have been shown to play redundant roles in essential developmental events. Added to lessons from cancer biology, it seems that the regulation of the cellular levels of a certain enzyme alone may not provide a secure enough mechanism for the developing cell to depend on for proper differentiation and development. Notably, the regulation of subcellular localization as well as cell type specific promoter occupancy of these enzymes and complexes provides an additional and plausibly essential layer of gene expression control [4].

Transcription factors, without enzymatic activity of themselves, bind to specific sequences of DNA, and interact and thus recruit complexes of proteins with proper enzymatic activity to control chromatin structure and integrity, further recruitment, assembly, or maintenance of regulator complexes, and/or recruitment or inhibition of recruitment of RNA polymerase II [5]. Transcription factors are thus to be regarded as scaffold proteins, and many of the other proteins in complexes regulating transcription are also non-enzymatic. In repression of transcription, examples of such non-enzymatic complex proteins are NCoR, SMRT, Sin3a and Groucho/TLE proteins [5]. Also smaller but powerful proteins, such as the LIM-only (LMO) proteins function as scaffold factors, and enzymatic proteins such as histone deacetylases are known to also exert non-enzymatic dependent function in transcription. It is conceivable that such extra-enzymatic functions are to provide the correct interfaces for proper complex assembly.

Hence, the levels and location of these "molecular pilots" thereby become absolutely critical for the correct assembly of complexes and guidance of the proper enzymatic activity to the right place at the right time.

Molecular pilots of cell cycle regulation

Cell proliferation, survival and death are likewise events depending on sequential activities by specific enzymes that are, at least in part, regulated by levels and subcellular localization of non-enzymatic assembly factors. Cell division is dependent on "checkpoint"-regulating cyclin-dependent kinases (CDKs), and the activities of these CDKs can be regulated by various mechanisms. These mechanisms include the regulation by non-enzymatic proteins that interact directly with cyclin–CDK complexes and inhibiting their activity. CDK inhibitors (CKI) include the so-called Ink4 family and the Cip/Kip family [6]. The Cip/Kip family of cell cycle inhibitors consists of three factors in mammals, p21Cip1, p27Kip1, and p57Kip2, and in this short review the roles for these proteins in the regulation of NSC proliferation and differentiation will be discussed.

The CKIs are functionally related to another family of non-enzymatic factors well known for their involvement in regulating cell death, namely the p53/p63/p73 family. These proteins are