Potassium Channels, Cell Cycle, and Tumorigenesis in the Central Nervous System

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SUMMARY

In addition to the well-understood role in action potential repolarization and control of brain homeostasis, potassium channels also play a fundamental role in controlling cellular proliferation. Here we wish to summarize evidence supporting potassium channels' involvement in tumorigenesis. We will first introduce basic concepts in cell cycle in the central nervous system, and then describe the multiple roles of potassium channels and their modulators in the central nervous system. Finally, we will focus on how brain tumors are controlled by potassium channel regulation, linking tumorigenesis process to cell cycle re-entry. We also introduce a novel possible modulator of potassium channels, and thus of tumorigenesis.

Key Words: Ion channels; potassium channels; cell cycle; tumors; CNS.

1. CELL CYCLE IN THE CENTRAL NERVOUS SYSTEM

In order for an organism to grow and survive, a proper balance between cell division, differentiation, and controlled cell death (apoptosis) is crucial. Cell cycle is a highly conserved mechanism by which eukaryotic cells proliferate. It is typically divided into four distinct phases: G1 (first gap), S (DNA synthesis), G2 (second gap), and M (mitosis); cells that exit the cell cycle are said to be in a quiescent (G0) state. Cell cycle progression is tightly regulated by control checkpoints, which ensure the correct completion of each phase before the progression to the next one.

A key role is played by cyclins (D, E, A, and B), cyclin-dependent kinases (CDKs), and their inhibitors (CDKIs), which are sequentially expressed to coordinate the orderly progression through cell cycle (1,2). The sequential activation/inhibition of different CDKs and their activity are regulated by several mechanisms, including growth factors and various signaling molecules (Rb, E2F, p21, p27, and p53). Passage beyond the restriction point in G1 is controlled by a number of complex transcription factors as well as the expression of cell cycle-related proteins (2,3). The E2F family of transcription factors plays a central role in regulating cellular proliferation by controlling gene expression (4). E2F activity is regulated in a cell cycle-dependent manner, principally through its association with the retinoblastoma tumor suppressor protein (Rb), which is in turn regulated by other CDKs and CDKIs. p53 is a tumor suppressor protein which is activated in response to cellular stress and prevents further progression through the cell cycle until cellular damage has been repaired.

If the cell has entered the S phase and is prepared to divide, programmed cell death occurs, preventing proliferation of damaged cells. In the brain, loss of p53 influences the cell cycle and therefore allows the survival of potentially damaged glial cells to proliferate (5). p21 is found downstream of p53 and is a universal inhibitor of CDKs; it binds to an extensive array of
cyclin/CDK complexes which are most pertinent to G\(_1/S\) phase arrest. p27 is another member of the CDKIs; it interacts with all subtypes of cyclin/CDK, causing cell cycle arrest in the G\(_1\) phase.

Developmentally, neural progenitor stem cells differentiate into neurons or glial cells over a protracted period (Fig. 1), and the mature phenotype of a cell is often determined postmitotically, or in adult stages. Cell cycle and cell fate determination are closely related events, and the same machinery and regulatory factors that govern the cell cycle are also fundamental to trigger cell differentiation (6,7). Specific cell cycle components differentially affect neuronal determination and differentiation: p27, for example, not only modulates various cyclins/CDKs complexes, but is also fundamental for the differentiation of glial retinal cells (6).

Apoptosis (or programmed cell death) and necrosis are fundamental for the normal development and function of multicellular organisms, balancing cell proliferation. Contrary to the necrotic process, apoptotic cells die in a controlled, regulated fashion. Several steps are characteristic of the apoptotic process: cell shrinkage, nuclear condensation, nuclear fragmentation, cell blebbing, and phagocytosis by macrophages. In the central nervous system (CNS), neuronal apoptosis is indispensable for a normal development, and the main function of this postnatal programmed cell death appears to be the adjustment of the number of neurons, possibly eliminating redundancy (8).

Interestingly, the cell cycle machinery shares some common participants with the apoptotic pathway, suggesting that both processes might share similar regulatory mechanisms. The decision to remain quiescent, resume active proliferation, or enter apoptosis is dictated by common extracelluar and intracellular factors (7). A diagrammatic representation of the major players involved in cell cycle re-entry and cellular proliferation is shown in Fig. 2.

In most brain regions, neurogenesis is generally confined to a discrete developmental period, during which neuronal precursor cells proliferate and differentiate into neurons and glial cells within designated germinal zones. Once the neuronal precursors exit the cell cycle and enter a postmitotic state, these cells migrate out of their proliferative zones and remain in a terminally

**Fig. 1.** Simplified model of differentiation of neural stem cells. Their fate is dependent on a number of factors involved in cell cycle regulation.