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T. Curran · Y. Christen (Eds.)

Two Faces of Evil: Cancer and Neurodegeneration

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Two Faces of Evil: Cancer and Neurodegeneration

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Editors

Two Faces of Evil: Cancer and Neurodegeneration

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Foreword

Homeostasis involves a delicate interplay between generative and degenerative processes to maintain a stable internal environment. In biological systems, equilibrium is established and controlled through a series of negative feedback mechanisms driven by a range of signal transduction processes. Failures in these complex communication pathways result in instability leading to disease. Cancer represents a state of imbalance caused by an excess of cell proliferation. In contrast, neurodegeneration is a consequence of excessive cell loss in the nervous system. Both of these disorders exhort profound tolls on humanity and they have been subject to a great deal of research designed to ameliorate this suffering. For the most part, the topics have been viewed as distinct and rarely do opportunities arise for transdisciplinary discussions among experts in both fields. However, cancer and neurodegeneration represent *yin–yang* counterpoints in the regulation of cell growth, and it is reasonable to hypothesize that key regulatory events mediated by oncogenes and tumor suppressor genes in cancer may also affect neurodegenerative processes. This was the rationale for organizing the *Colloques Médecine et Recherche*, April 26, 2010 on the topic of *Two Faces of Evil: Cancer and Neurodegeneration*.

The presentations by the leaders of both fields were full of exciting unpublished data that reaffirmed the connection between the disciplines. Remarkably, genes that affect cell cycle progression and checkpoint control also play specific roles in postmitotic neurons that influence neurodegeneration. Many oncogenic signaling pathways have been expropriated to fulfill distinct functions in a range of biological situations. The complexity of the nervous system is such that evolution has usurped most molecular, biochemical and cellular regulatory mechanisms to support the formation, function and maintenance of neurons. The discussions at the meeting transcended traditional boundaries. Several new concepts were shared that will stimulate future research and perhaps contribute to better therapies for cancer patients as well as those struggling with the ravages of neurodegeneration.

Acknowledgments

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Updating the Mammalian Cell Cycle: The Role of Interphase Cdks in Tissue Homeostasis and Cancer

Mariano Barbacid

Abstract Genetic interrogation of the mammalian cell cycle has revealed that the essential role of interphase Cdks is not to specifically drive the various phases of the cycle, as previously proposed in widely accepted models, but to sustain proliferation of specialized cells at various times during embryonic or postnatal development. Indeed, genetic studies have indicated that Cdk1 can drive the mammalian cell cycle in the absence of interphase Cdks. The molecular bases for the essential requirement of interphase Cdks in selected cell types are still poorly understood. However, these observations have important implications for understanding the role of Cdk misregulation in cancer. Indeed, it is likely that misregulation of Cdks may only confer proliferative advantages to selected cell types. More importantly, it is also possible that certain cells may become dependent of selective interphase Cdks only when their proliferation is driven by defined oncogenes. Recent studies have illustrated the requirement for Cdk4 in HER2-overexpressed mammary adenocarcinomas and K-Ras oncogene-driven lung adenocarcinomas but not in the corresponding normal tissues. Likewise, Cdk2 plays an important role in the development of Myc-induced lymphomas. These findings may open the door to the design of novel therapeutic strategies that may benefit cancer patients.

Molecular analysis of human tumors has revealed that most carry mutations that result in misregulation of the cell cycle. Tumor cells accumulate mutations that result in unscheduled cell proliferation, either by constitutive activation of mitogenic signaling pathways or by elimination of regulatory anti-mitogenic signals (Malumbres and Barbacid 2001; Massague 2004). In addition, most tumors acquire genomic instability as a consequence of alterations in cell cycle checkpoints (Kastan and Bartek 2004) and chromosome instability due to errors during the mitotic phase of the cycle (Kops et al. 2005; Fig. 1). Progression through the cell cycle is driven by heterodimeric kinases made up of a regulatory subunit, known as

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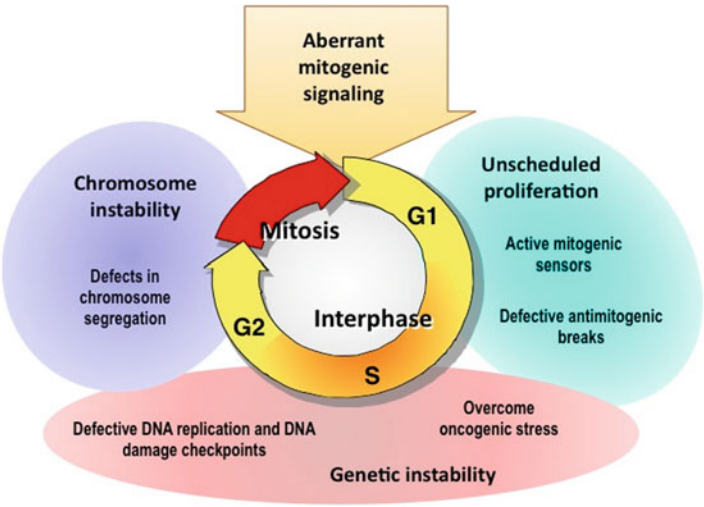

Fig. 1 Schematic diagram of the mammalian cell cycle with those defects implicated in human cancer

Cyclin, and a catalytic subunit, designated as Cyclin-dependent kinase or Cdk. This designation stems from the fact that this catalytic subunit is completely inactive in the absence of its corresponding activating subunit, the Cyclin. Cdks are constitutively expressed during the cycle. In contrast, Cyclins are synthesized and destroyed at specific phases, thereby regulating kinase activity in a timely manner during the cell cycle (Malumbres and Barbacid 2001).

Mammalian cells express multiple Cyclin and Cdks, although not all of them are involved in driving the cell cycle (Malumbres and Barbacid 2005). Among the Cdks, only five, Cdk1, Cdk2, Cdk3, Cdk4 and Cdk6, are thought to directly participate in cell cycle regulation. Cdk7 also plays an important role in the cell cycle since this kinase is responsible for activating Cdk1 and possibly Cdk2. Whereas Cdk1 is generally considered to be "the" mitotic kinase, the other Cdks are believed to play specific roles in the distinct phases of cell division that constitute the interphase, that is, the period between two mitotic events in proliferating cells (see below). Among these kinases, only Cdk4 has been found to be mutated in human cancer, and only in a few cases of hereditary melanoma (Wölfel et al. 1995). In addition, Cdk6 overexpression has been documented in lymphomas, leukemias and melanomas as a consequence of chromosomal translocations. However, Cdk activity can be altered in human cancer by several independent mechanisms, including increased levels of Cyclin expression or impaired degradation that result in increased availability of these regulatory subunits. Increased Cdk activity can also result from loss of members of the INK4 and CIP/KIP families of Cdk inhibitors. Whereas INK4 proteins bind directly to the Cdk catalytic subunits, preventing their interaction with their cognate Cyclins, the CIP/KIP inhibitors

bind to Cdk/Cyclin heterodimers, forming inactive tertiary complexes (Malumbres and Barbacid 2001; Massague 2004).

Little is known about the full spectrum of physiological substrates of the interphase Cdk/Cyclin complexes. However, the role of these kinases in inactivating the pocket proteins – RB, p107 and p130 – has been profusely illustrated (Classon and Harlow 2002). These proteins function as constitutive repressors of the cell cycle machinery in quiescent cells. Tumor-associated alterations frequently deregulate these Cyclin–Cdk complexes, resulting in constitutive inactivation of the pocket proteins and allowing either continued proliferation or unscheduled re-entry into the cell cycle, two properties characteristic of almost every human cancer cell (Malumbres and Barbacid 2001).

1 Mammalian Cdks and the Classical Cell Cycle Model

The basic regulation of the cell cycle by Cdk/Cyclin complexes was first established in yeasts. In these unicellular organisms, cell cycle progression is driven by a single Cdk – Cdc28 and Cdc2, the orthologs of mammalian Cdk1 – that binds sequentially to various Cyclins at different stages of the cycle (Nurse 1997). In mammals, the number of Cdks and Cyclins implicated in the control of cell cycle progression has increased considerably (Malumbres and Barbacid 2005). According to a widely accepted model for the mammalian cell cycle, these additional Cdks, generated throughout evolution, have acquired unique specific roles during interphase by overtaking the roles played by Cdc28/Cdc2 during interphase and limiting Cdk1 activity to the mitotic phase (Fig. 2). This model has been primarily derived from biochemical evidence mostly gathered from studies carried out with human tumor cells grown in culture for many generations. Unfortunately, recent genetic evidence has proven to be incompatible with some key tenants proposed by the classical model.

According to this model, Cdk/Cyclin complexes containing the mammalian interphase Cdks – Cdk2, Cdk3, Cdk4 and Cdk6 – (Cdk5 plays a specific role in the brain and will be discussed in other chapters) bound to their cognate Cyclins act in a sequential and orderly fashion during the various events known to take place during interphase. That is, this model replaces the basic yeast cell cycle model in that the kinases responsible for driving the cell cycle are made up of different catalytic and regulatory subunits instead of a single catalytic subunit (Cdc28/Cdc2) sequentially bound to the different Cyclins (Fig. 2). According to this model, mitogenic signals are first sensed by inducing expression of D-type Cyclins (D1, D2 and D3) that bind and activate Cdk4 and Cdk6 during G1, a phase of the cell cycle in which cells prepare to initiate DNA synthesis. Recent evidence obtained in our laboratory has indicated that this concept may have to be revised, since non-proliferating cells with impaired mitogenic signaling due to ablation of the three Ras proteins express even higher than normal levels of Cyclin D1 (Drosten et al. 2010). Regardless of the mechanism by which D-type Cyclins are induced, they bind to and activate Cdk4 and/or Cdk6, which in turn