Interactions Between Myc- and Cyclin-Dependent Kinase Inhibitors in Cancer

Kirsteen H. Maclean, PhD, and John L. Cleveland, PhD

Summary

Deregulated cell growth and the inhibition of apoptosis are hallmarks of cancer. The MYC family of oncogenes are pivotal players in tumorigenesis and are altered in most tumor types. c-Myc is the founding member of a family of structurally related basic helix-loop-helix-leucine zipper (bHLH-Zip) proteins that function as sequence-specific transcription factors and are aberrantly expressed in most cancers. c-Myc is a key regulator of cell proliferation and differentiation, and its expression is both necessary and sufficient to drive quiescent cells into S phase. Following mitogenic stimulation, c-Myc is rapidly induced; remains elevated throughout the cell cycle and, through dimerization with its bHLH-Zip partner Max, regulates the transcription of genes essential for cell growth and division. Conversely, c-Myc expression is rapidly suppressed by growth inhibitory signals such as transforming growth factor β. However, these controls are lost in cancers by translocations, amplifications, and alterations in regulatory signaling pathways, resulting in abnormally high levels of MYC oncoproteins. The precise roles that Myc oncoproteins provide to provoke tumorigenesis are not fully resolved but do include the regulation of target genes that control cell division, differentiation, cell size, and angiogenesis. These target genes include members of the cyclin dependent kinase inhibitors (encompassing the Ink4 family and the Cip/Kip family of inhibitors), responsible for inhibiting the activity of cyclin/cyclin-dependent kinase complexes that regulate cell cycle traverse. The regulation of these inhibitors by Myc clearly represents an important target in cancer prevention and therapeutics.

Key Words: Myc, CDK, CDK inhibitors, Cyclins, Ink4, Cip/Kip.

1. INTRODUCTION

The genomic integrity of multicellular organisms is ensured by various components of the DNA repair machinery and/or by the decision of cells to undergo apoptosis or senescence. Collectively, these programs prevent cells that have accumulated DNA...
mutations from developing into cancer cells. Once thought to simply provide a proliferative advantage to the malignant cell, the activation of oncogenes is now recognized to also provide new avenues for cancer therapeutics. Foremost among these potential targets are the Myc family of oncogenes (c-Myc, N-Myc, and L-Myc) that function as master regulatory transcription factors overexpressed in approximately 70% of all human cancers (1-4). The array of functions executed by Myc oncoproteins underscore their importance in tumor cell biology, as their enhanced expression drives unrestricted cell proliferation and increases in cell mass and ribosome biogenesis (4,10), inhibits terminal differentiation programs (11,12), and provokes tumor angiogenesis (13,14). Paradoxically, in normal cells, Myc overexpression triggers the apoptotic program (15,16), which acts as a defense mechanism against transformation, and Myc also promotes genomic instability (17). Collectively, these events safeguard cancer cells from progressing toward overt malignancy. Furthermore, Myc functions appear necessary to maintain the tumorigenic state, as even brief inactivation of Myc causes rapid tumor regression because of the induction of apoptosis (17,18). Thus, Myc is widely viewed as an important target in both cancer chemoprevention and cancer therapeutics.

On the flip side of cell growth control are a series of dedicated inhibitors that function to hold the cell cycle in check by inhibiting the activity of cyclin/cyclin-dependent kinase (Cdk) complexes (cyclin D/Cdk4;Cdk6, cyclin E/Cdk2, cyclin A/Cdk2, and cyclin B/Cdk1) that normally phosphorylate key substrates to allow entry and progression through the cell cycle. Cdk inhibitors fall broadly into those that specifically target cyclin-D/Cdk4;Cdk6 complexes, the Ink4 family of inhibitors (p16Ink4a, p15Ink4b, p18Ink4c, and p19Ink4d), and those that broadly inhibit all Cdks, the Cip/Kip family (p21Cip1, p27Kip1, and p57Kip2). Notably, at least two of the Inks, p18Ink4c and p16Ink4a, as well as p27Kip1 play essential roles as guardians against tumorigenesis. For example, gene targeting has established that mice lacking p16Ink4a, p18Ink4c, or p27Kip1 are tumor-prone, especially when exposed to mutagens (19-23). Furthermore, deletion or silencing of the INK4A locus and the suppression of INK4B, INK4C, and KIP2 expression are common features of many human malignancies (24-28). In addition, the suppression or loss of heterozygosity (LOH) of KIP1 is a well-established predictor of poor prognosis in many human cancers (24-32). Finally, there are now obvious connections between Myc and many of the Cdk inhibitors in tumorigenesis. Herein, we describe these interactions and their relevance for tumorigenesis and cancer therapy.

2. MYC’S TRANSCRIPTION FUNCTIONS

Initial studies by Bishop and Varmus and colleagues demonstrated that v-Myc was the oncogene of the avian myelocytomatosis (MC29) retrovirus. Subsequent work then revealed that v-Myc’s cellular homolog c-Myc, as well as the other Myc family members N-Myc and L-Myc, is activated by chromosomal translocations or amplifications in many human cancers (including breast and prostate, lymphoma, leukemia, colon and cervical carcinoma, melanoma, glioblastoma, and small-cell lung carcinoma). Furthermore, Myc genes are often overexpressed in cancers having mutations in other signaling pathways and in those having mutations in tumor suppressors such as p53, which negatively regulate Myc expression (33).