Preface

The devotion of this volume to the role of D-type cyclins in tumorigenesis is reflective of the central role that these cell-cycle regulatory proteins play in the generation and maintenance of a vast array of human malignancies. This family of proteins has been and continues to be the subject of a voluminous primary and review literature over 25 years, and cyclin D1 in particular stands among auspicious company (e.g., ras, myc, p53) as one of the most common central drivers of cancer. This collection of reviews and opinions is meant to present a historical perspective of the work that led to the discovery and biological insight into the key roles for the D-type cyclins in normal cellular processes and disease and the clinical targeting of its enzymatic partners cdk4 and cdk6. Perhaps more importantly, several additional chapters provide summaries of important, recent advances in understanding a much more complex regulation of cyclin D1 production and function that was initially appreciated, as well as roles for the D-type cyclins that extend well beyond their function as cdk activators and/or extend the understanding of cyclin D/cdk function outside of its commonly accepted role as a driver of the G1-to-S phase transition in cycling cells.

As elegantly articulated in the first chapter from Sherr and Sicinski, the origin story of the D-type cyclins, identified over two and a half decades ago, includes a rather unusual element of "instant" appreciation for the central role of these proteins in both cell-cycle control and cancer. That is, D-type cyclins were initially discovered by Matsushime (working in the Sherr lab) as mediators of cell proliferation signals emanating from outside the cell and transduced by growth factor receptors on the cell surface, immediately suggesting a role for D-type cyclins in connecting nuclear events to the sensing of the cell's environment. Contemporaneously, the mammalian D-type cyclins were shown to complement yeast mutants deficient for their own cyclins (Xiong and coworkers), giving biological support to functional inferences drawn from interspecies and interfamily protein homology, and importantly, cyclin D1 was also identified as the likely target of chromosomal rearrangement in parathyroid tumors (Motokura and coworkers). Thus, within a short span of time, researchers using the most cutting-edge functional assays of the period identified the same proteins as likely mammalian G1-phase cyclins that were critical for transducing growth signals from growth factor receptors and that were in at least

one instance (and subsequently appreciated to be much more widely observed) the direct target of genetic oncogenic events. The sum of these discoveries was the generation of a hypothesis that continues to be tested and explored to this day – a central regulator of cellular decisions to proliferate (or not) that acts as an obligate partner of specific members of the cyclin-dependent kinase family is commonly exploited by tumor cells ostensibly to remove the dependence of the cell on upstream signaling events, thus freeing the cell to divide at will, producing neoplasms in a wide variety of tissues.

Despite this rapid start to the appreciation of D-type cyclins as key instigators of normal and aberrant cellular proliferation, the study of exactly how they and their partner cdks effect these biological responses has spanned the subsequent two decades and continues to this day. Initial functional studies in cells, and importantly in a wide variety of genetically engineered mice, strongly supported the perceived roles of D-type cyclins as decision-makers in the cell cycle in normal cells and in tumors. These studies are summarized in the chapter from Kalaszczynska and Ciemerych and importantly point out the repeated finding that deficiencies in D-type cyclins produce deficiencies in the development of normal tissues. This in turn provided clues to the proclivity of tumors to deregulate D-type cyclins: perhaps the lack of control engendered by amplifications, rearrangements, and mutations of this family of proteins locks certain cells in a more embryonic state, providing the seeds for subsequent generation of tumors.

Several following chapters then explore the function and regulation of D-type cyclins in molecular detail – from the finding that isoforms of cyclin D1 generated posttranscriptionally that evade normal regulatory controls may be key to oncogenesis in many tumors (Diehl and Knudsen) to an expansion of the understanding of functions of D-type cyclins that extend well beyond their canonical roles as regulators of the retinoblastoma protein (pRB), the best understood substrate of D cyclin/cdk4(6) complexes, and the function that is presumed to be key to the success of cdk4/6 inhibitors that are currently in clinical use. Examples of these functions extend to direct roles in transcriptional control (with or without partner cdks; DiSante et al.) and to a role in nutrient sensing and metabolism that may dictate important physiological responses to loss of D cyclin/cdk function and that may be key to future combinatorial therapies designed to push malignant cells into a state that favors their elimination versus stasis (Valenzuela and Brown).

The volume ends with a provocative chapter from Dowdy summarizing work that redefines the fundamental role of the cyclin D/cdk4(6) complex as a modifier of pRB function. Here, the author expounds on recently published evidence that intriguingly suggests that cyclin D/cdk4(6) complexes may function to produce a sort of "pRB code" by modifying one and only one of some 14 individual phosphoacceptor serines or threonines in pRB, such that a cell entering G1 from a resting state may express any or all of 14 different subspecies of pRB distinguished by phosphorylation on one of these residues. Importantly, these cyclin D-stimulated modifications of pRB seem to favor the association of pRB with its downstream targets, rather than disrupt them, as the canonical model of cyclin D1 function now posits. The biological implications of this study are multifold and include the

hypothesis that the oncogenic function of D-type cyclins may not involve pRB inactivation per se, but rather may focus on one of the other functions described above, such as metabolic control or kinase-dependent transcriptional regulation (depending on cell type?) that favors exit from a resting state (or failure to enter a resting state, such as that accompanying the process of differentiation). Clearly, the story of the D-type cyclins is far from fully written, and the work described in this volume, produced in numerous labs over many years, will continue to help reveal and refine the normal and tumorigenic functions of these proteins. This in turn will ultimately improve our understanding of cell-cycle regulation, tissue formation in development, and, importantly, the best way to employ exciting new therapeutics targeting these proteins in human cancers.

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http://www.springer.com/978-3-319-64451-6

D-type Cyclins and Cancer
Hinds, P.W.; Brown, N.E. (Eds.)
2018, IX, 152 p. 29 illus., 25 illus. in color.,
ISBN: 978-3-319-64451-6
A product of Humana Press