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Cyclin E as a potential therapeutic target in high grade serous ovarian cancer

J. Kanska [1], M. Zakhour [1], B. Taylor-Harding, B.Y. Karlan, W.R. Wiedemeyer *

Women's Cancer Program, Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA 90048, USA

HIGHLIGHTS

- The *CCNE1* gene is amplified in 20% of ovarian high grade serous carcinomas (HGSC) & is associated with platinum resistance.
- Cyclin E1 is a regulatory subunit of cyclin dependent kinases (CDK), which are potential targets for therapy.
- Further study on therapeutic options for the cyclin E1-amplified subset of HGSC is warranted.

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ABSTRACT

Cyclin E1 (*CCNE1*) gene amplification occurs in approximately 20% of ovarian high grade serous carcinoma (HGSC) and is associated with chemotherapy resistance and, in some studies, overall poor prognosis. The role of cyclin E1 in inducing S phase entry relies upon its interactions with cyclin dependent kinases (CDK), specifically CDK2. Therapies to target cyclin E1-related functions have centered on CDK inhibitors and proteasome inhibitors. While many studies have helped elucidate the functions and regulatory mechanisms of cyclin E1, further research utilizing cyclin E1 as a therapeutic target in ovarian cancer is warranted. This review serves to present the scientific background describing the role and function of cyclin E1 in cancer development and progression, to distinguish cyclin E1-amplified HGSC as a unique subset of ovarian cancer deserving of further therapeutic investigation, and to provide an updated overview on the studies which have utilized cyclin E1 as a target for therapy in ovarian cancer.

1. Introduction

As one of the most frequently occurring genetic alterations, amplification of the *CCNE1* gene is found in about 20% of ovarian HGSC [1]. Amplification-associated overexpression of cyclin E1 drives cell cycle progression and correlates with resistance to platinum-based therapeutic agents [2,3]. Genetic and biochemical studies have established cyclin E1 as a regulator of the retinoblastoma (RB) tumor suppressor pathway. Cyclin E1 binds and activates members of the cyclin-dependent kinase (CDK) family of proteins, which then phosphorylate and inactivate the RB protein, and other closely related pocket proteins, p107 (*RBL1*) and p130 (*RBL2*) [4]. RB is a central regulator of cell cycle progression through its inhibitory effect on E2F transcription factors, which in turn regulate key genes involved in the G_1 to S phase transition of the cell cycle [5]. RB pathway deregulation results in unrestricted proliferation, which is considered a hallmark of cancer [6].

Human cyclin E1 was initially discovered in a cDNA screen in *Saccharomyces cerevisiae* as one of several human genes that can complement for loss of yeast interphase cyclins, CLN-1, CLN-2 and CLN-3, and initiate START (G_1 to S transition in yeast) [7]. Cyclin E1 can physically interact with *S. cerevisiae* CDC28 or its human homolog CDC2 (cyclin-dependent kinase 1, CDK1) and activate its kinase activity, a requirement for G_1-S transition in the yeast system [8]. Subsequent publications have established that in human cells, cyclin E1 protein expression and its associated CDK activity are highly cell cycle-dependent, peaking in late G_1 and reaching their nadir in G_2-M and early G_1 [4]. Moreover, these studies have identified CDK2 as the main binding partner of cyclin E1, whereas a relatively small fraction of cyclin E1 was shown to associate with CDK1.

Consistently between all studied systems, cyclin E1-associated kinase activity integrates a number of regulatory signals and plays a crucial role in determining whether or not to initiate S phase. Complex regulatory mechanisms both at the transcriptional and post-translational levels mediate cell cycle phase-dependent expression of cyclin E1 (Fig. 1 and Supplemental Fig. 1). Here, we will review the role of cyclin E1 as a putative oncogene in ovarian cancer and other malignancies and

* Corresponding author at: 8700 Beverly Blvd, D-3092, Los Angeles, CA 90048, USA.
E-mail address: wiedemeyerw@cshs.org (W.R. Wiedemeyer).
[1] Co-first authors.

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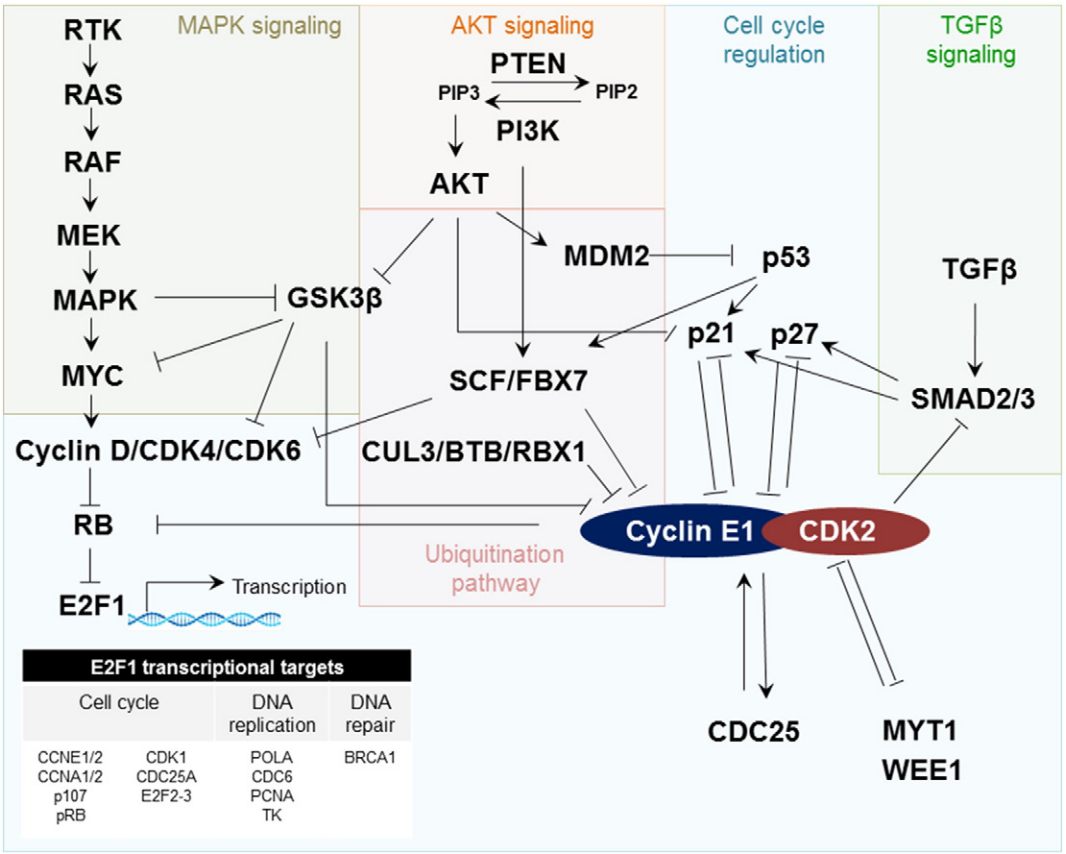

Fig. 1. Regulatory mechanisms that mediate cell cycle phase-dependent expression of cyclin E1 and induction of E2F target genes. RTK: receptor tyrosine kinase. Definitions of abbreviations can be found in Supplemental Fig. 1.

provide an overview of therapeutic options to target cyclin E1-CDK signaling.

2. Regulation of cyclin E1

E-type cyclins demonstrate high oncogenic potential and their amplification can induce tumor formation both in vivo and in vitro. Their expression in normal cells is tightly regulated to assure controlled cell proliferation during development and homeostasis. The human genome encodes two cyclin E homologs, *CCNE1* and *CCNE2*, which are translated into protein products of molecular weights 47.07 and 46.75 kDa, referred to as cyclin E1 and cyclin E2, respectively. These cyclins have a high degree of homology within the conserved regions responsible for CDK and CDK inhibitor (CDKi) interactions, as well as within Nuclear and Centrosomal Localization Sequences (NLS and CLS) [9]. Earlier research suggested that both E-type cyclins are redundant, however further studies revealed that they have different expression patterns and cell type-specific functions, e.g. in endoreplication and meiosis [10,11]. In addition, both homologs were shown to be independently regulated by diverse sets of transcription factors and microRNAs [12,13]. In this review, we will focus primarily on cyclin E1, which has been studied more extensively and is more frequently amplified in cancer than cyclin E2. Cyclin E2 may be upregulated in tumors independently of cyclin E1 and has been reported to be frequently amplified in recurrent carcinomas [14]. Similar to cyclin E1, cyclin E2 overexpression is associated with increased proliferation, invasion, and drug resistance [15].

Multiple activating and inhibitory inputs are in place to maintain cyclin E1 oscillation during each cell division. At the transcriptional level, c-Myc and E2F are key regulators of *CCNE1* expression, and both activate cyclin E1 via distinct molecular pathways [16]. c-Myc is a known proto-oncogene which is upregulated by mitogenic stimuli. Early in the G_1 phase of the cell cycle, increases in c-Myc levels promote transcription of genes responsible for cell cycle progression, such as *CCND2* (cyclin D2) and *CDK4*. D-type cyclins later bind and activate CDK4 and CDK6, leading to phosphorylation of their target proteins. One of the key targets of cyclin D/CDK complexes is the pocket protein family, which includes retinoblastoma (RB) and its close relatives, p130 and p107. The central role of these proteins is to protect the cell from entry to the S phase and replicating its DNA until it is ready for mitosis. Hence, RB acts as a tumor suppressor, which, in the absence of cyclin D and cyclin E/CDK complexes, is able to maintain cells in the G_1/G_o phase through binding and inhibiting transcriptional activity of E2F proteins. Upon RB hyper-phosphorylation by cyclin D/CDK complexes, E2Fs are released from the inhibitory complex and can initiate transcription of genes which promotes S phase entry, such as *CCNE1*, *CCNE2*, *CCNA*, and histone proteins [17]. *CCNE1* expression is activated by E2F1, E2F2 and E2F3 proteins and suppressed by the inhibitory E2Fs, such as E2F4, E2F5, and E2F6 [18]. Once activated, cyclin E1/CDK2 becomes independent of mitogenic stimuli and can upregulate its own expression by further phosphorylating and dissociating RB/E2F complexes [17].

Furthermore, cyclin E1/CDK complexes can be silenced by a number of post-transcriptional regulatory mechanisms, such as *CCNE1* promoter silencing, protein inhibition by CDKIs ($p21^{Cip1}$ and $p27^{Kip1}$), degradation by the SCF^{Fbw7} tumor suppressor pathway, and microRNA-mediated inhibition of cyclin E1 synthesis (miR-15a, miR-15b, miRNA-16) [9,12]. Like *CCNE1*, miR-15 and miR-16, which are critical regulators of gene expression in normal cells, are also direct targets of E2F1 transcriptional activity, and possibly participate in the feed-forward loop, which negatively regulates cell cycle progression via the cyclin E1/E2F1 axis [19]. The importance of RB pathway inactivation for cancer development is highlighted by the near-universal presence of genomic aberrations targeting this pathway in HGSC and other cancers [20]. Mutation or deletion of *RB1*, $p16^{INK4A}$ (*CDKN1A*), or amplification of *CCND1*, *CDK4*, *CCNE1*, or E2F genes are distinct mechanisms of RB pathway inactivation