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Review Article

A Seroprevalence Study of Varicella Zoster Virus Among Healthcare Workers in A Tertiary Care Setting

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Received Date: September 25, 2025; **Accepted Date: October 01, 2025; Published Date: October 15, 2025**

Citation: C.S.Botenne, S.De Silva, D.R.T. Jayasundara, B.Samaraweera, J.I Abeynayake, (2025), A Seroprevalence Study of Varicella Zoster Virus Among Healthcare Workers in A Tertiary Care Setting, *Clinical Trials and Clinical Research*,4(5); **DOI:**10.31579/2834-5126/114

Abstract

Cyclin E is a vital regulator in the cell cycle, primarily governing the transition from the G1 phase to the S phase. By partnering with cyclin-dependent kinases (CDKs), it orchestrates a series of phosphorylation events that drive cell cycle progression. However, dysregulation of Cyclin E expression and activity is frequently observed in various pathological conditions, especially cancers, contributing to uncontrolled cell proliferation and tumorigenesis. This review comprehensively summarizes the structural features, biological functions, roles in disease development, and current therapeutic approaches related to Cyclin E. Gaining in-depth insights into Cyclin E's mechanisms can offer a solid theoretical foundation for the development of more effective and targeted therapeutic strategies.

Keywords: cyclin e; cell cycle; cancer; targeted therapy; disease

Abbreviations

ACIP- Advisory Committee on Immunization Practices β- Beta Coefficient

CDC- Centers for Disease Control and Prevention CI-Confidence Interval

DF- Degree of Freedom

ELISA- Enzyme Linked Immunosorbant Assay EXP(B)- Odds Ratio

HCW- Health Care Worker ICU- Intensive Care Units IgG- Immunoglobulin G IQR- Inter Quartile Range IU- International Units

LRH- Lady Ridgeway Hospital

MMWR- Morbidity & Mortality Weekly Report NHSL- National Hospital of Sri Lanka

OR-Odds ratio p- Probability

PBU- Premature Baby Care Units RR- Relative Risk

SE-Standard Error

SD- Standard Deviation

SJGH-Sri Jayewardenapura General Hospital SOP- Standard Operating Procedure

VZV-Varicella Zoster Virus

Highlights

- Seroprevalence of Varicella Zoster among study participants was 66.8%
- Seropositivity is significantly associated with age.
- Past history of infection or vaccination increases the likelihood of being seropositive.

1.Introduction

The cell cycle is a highly coordinated process that ensures proper cell growth, division, and maintenance of tissue homeostasis. Cyclin E, as a key member of the cyclin family, plays a pivotal role in regulating the critical transition from the G1 phase to the S phase, where DNA replication occurs. Upon binding to its cognate cyclin-dependent kinases, mainly CDK2, Cyclin E forms active kinase complexes that phosphorylate numerous downstream targets. In normal cells, the expression and activity of Cyclin E are tightly regulated by a variety of internal and external signals. Nevertheless, in pathological states, particularly in cancers, the delicate balance of Cyclin E regulation is disrupted, leading to abnormal cell cycle progression and contributing significantly to disease development. Exploring the functions, mechanisms, and therapeutic implications of Cyclin E is of great significance for understanding disease pathogenesis and formulating innovative treatment strategies.

2. Structure of Cyclin E

2.1 Domain structure

Cyclin E possesses a characteristic structural architecture. It contains a conserved cyclin box, which is approximately 100 amino acids long and serves as the binding site for CDK2. The cyclin box folds into an α-helical structure that precisely fits into the corresponding groove on CDK2, enabling the formation of the Cyclin E-CDK2 complex. In addition to the cyclin box, Cyclin E has an N-terminal region and a C-terminal region. The N-terminal region often contains regulatory motifs that can be modified by phosphorylation, acetylation, or other post-translational modifications, which in turn affect the stability and activity of Cyclin E. The C-terminal region may participate in protein-protein interactions, influencing the subcellular localization and functional regulation of the Cyclin E-CDK2 complex [1].

2.2 Structural insights from crystallography

X-ray crystallography and cryo-electron microscopy studies have provided detailed structural information about the Cyclin E-CDK2 complex. These structural analyses have revealed the precise molecular interactions between Cyclin E and CDK2 during complex formation. They show how Cyclin E binding induces conformational changes in CDK2, exposing the active site and enhancing its kinase activity. The structural insights also help in understanding the interactions between the Cyclin E-CDK2 complex and its substrates, laying a foundation for the rational design of small molecule inhibitors that can disrupt the complex or inhibit its kinase activity [2].

3. Biological functions of Cyclin E

3.1 Regulation of the cell cycle

The primary function of Cyclin E is to drive cells from the G1 phase into the S phase. As cells approach the G1/S transition, the expression of Cyclin E gradually increases. The newly synthesized Cyclin E binds to CDK2, forming the active Cyclin E-CDK2 complex. This complex phosphorylates key substrates, such as the retinoblastoma protein (Rb). Phosphorylation of Rb leads to the release of the transcription factor E2F, which then activates the transcription of genes required for DNA replication, including those encoding DNA polymerases, helicases, and other replication factors. Cyclin E also plays a role in coordinating the assembly of the pre-replication complex, ensuring the accurate initiation of DNA replication. Moreover, it can integrate various extracellular and intracellular signals, such as growth factor signaling and DNA damage responses, to finely tune the G1/S transition [3].

3.2 Non-cell cycle functions

Beyond its role in cell cycle regulation, Cyclin E has been reported to have non-cell cycle functions. It can participate in the regulation of gene transcription. The Cyclin E-CDK2 complex can phosphorylate transcription factors other than Rb, influencing the expression of genes involved in cell metabolism, angiogenesis, and cell adhesion. In addition, Cyclin E has been implicated in the regulation of centrosome duplication. Centrosomes are essential for proper spindle formation and chromosome segregation during cell division. Dysregulation of Cyclin E can lead to abnormal centrosome duplication, which may contribute to genomic instability [4].

4. Cyclin E in diseases

4.1 Cancers

Dysregulation of Cyclin E is a common occurrence in many types of cancers. Overexpression of Cyclin E is frequently observed in breast cancer, lung cancer, and ovarian cancer. In breast cancer, high levels of Cyclin E are associated with tumor progression, poor prognosis, and resistance to chemotherapy. Amplification of the CCNE1 gene, which encodes Cyclin E1, can lead to excessive production of Cyclin E, resulting in hyperactivation of the Cyclin E-CDK2 complex. This hyperactivity promotes continuous cell cycle progression, bypassing normal growth control mechanisms and driving tumor cell proliferation. Moreover, abnormal Cyclin E expression can contribute to cancer cell invasion and metastasis by modulating the expression of genes related to cell motility and extracellular matrix remodeling [5].

4.2 Other diseases

Cyclin E is also involved in non-cancerous diseases. In neurodegenerative diseases, such as Alzheimer's disease, abnormal regulation of Cyclin E has been reported. In neurons, dysregulated Cyclin E expression may disrupt normal cell cycle processes, leading to neuronal apoptosis and cognitive decline. In cardiovascular diseases, Cyclin E plays a role in the regulation of vascular smooth muscle cell proliferation. Dysregulation of Cyclin E can contribute to the abnormal proliferation of smooth muscle cells in the arterial wall, which is an important process in the development of atherosclerosis [6].

5. Therapeutic strategies targeting Cyclin E

5.1 Small molecule inhibitors

Small molecule inhibitors targeting the Cyclin E-CDK2 axis have become a focus of drug development. Some inhibitors are designed to bind to the ATP-binding pocket of CDK2, preventing the phosphorylation of downstream substrates and blocking cell cycle progression at the G1/S transition. For example, flavopiridol, an early CDK inhibitor with activity against multiple CDKs including CDK2 associated with Cyclin E, has shown potential in preclinical studies. However, its clinical application has been limited by toxicity and issues related to selectivity. Currently, more selective small molecule inhibitors of Cyclin E-CDK2 are being developed, aiming to specifically target the abnormal activity of this complex in cancer cells while minimizing effects on normal cells [7].

5.2 Antibody-based therapies

Antibody-based approaches targeting Cyclin E are emerging as potential therapeutic strategies. Monoclonal antibodies can be engineered to specifically bind to Cyclin E, blocking its interaction with CDK2 or promoting its degradation. These antibodies can also be conjugated with cytotoxic payloads to directly kill cells with dysregulated Cyclin E expression. Although still in the preclinical and early clinical development stages, antibody-based therapies offer the advantage of high specificity, potentially providing more targeted treatment compared to small molecule inhibitors [8].

5.3 Combination therapies

Combination therapies that combine Cyclin E-CDK2 inhibitors with other anti-cancer agents or treatment modalities are being actively explored. For instance, combining CDK2 inhibitors with DNA-damaging chemotherapy drugs may enhance the sensitivity of cancer cells to treatment by disrupting the cell cycle and interfering with DNA repair mechanisms. Additionally, combining Cyclin E-targeted therapies with immunotherapies may modulate the tumor microenvironment and enhance anti-tumor immune responses. In non-cancer diseases, combination therapies involving Cyclin E regulation along with other disease-specific treatments may also offer more effective therapeutic options [9].

6. Challenges and future directions

Despite the progress in Cyclin E-targeted therapy, several challenges remain. One major challenge is the development of resistance to inhibitors in cancer cells. Resistance mechanisms may include upregulation of alternative cyclin-CDK complexes, mutations in CDKs or associated regulatory proteins, and activation of compensatory signaling pathways. Understanding these resistance mechanisms and developing strategies to overcome them are crucial for improving treatment efficacy. Another challenge is the potential off-target effects of small molecule inhibitors, which may affect normal cells with high proliferative activity. Developing more selective and less toxic inhibitors is an important goal. In the future, further research on the non-cell cycle functions of Cyclin E may uncover new therapeutic targets and strategies. The application of advanced technologies, such as artificial intelligence in drug design and high-throughput screening, may accelerate the discovery of novel Cyclin E-targeted drugs and combination therapies.

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