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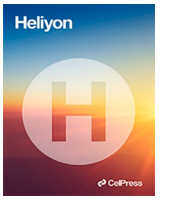

Review article

The role of cell cycle-related genes in the tumorigenesis of adrenal and thyroid neuroendocrine tumors

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ABSTRACT

The molecular mechanisms underlying adrenal and thyroid neuroendocrine tumors, including their tumorigenesis, progression, and metastasis, involve unique pathways regulating cell cycle progression. To better understand these mechanisms and pathways, extensive in-depth research on cell cycle-related genes is necessary. This review aims to describe and interpret current single-cell RNA sequencing studies on neuroblastoma, medullary thyroid cancer, and pheochromocytoma tumors. Our review summarizes differentially expressed cell cycle-related genes with distinct functions, highlighting their potential as therapeutic targets and components of panels used to determine tumor type or aggressiveness. Although some insights have been gained, there is still limited information on these topics, and further research is required to explore the regulatory mechanisms of these tumors.

1. Introduction

Neuroendocrine tumors (NETs) are complex and heterogeneous tumors that are believed to arise from specialized neuroendocrine (NE) cells. These cells contain secretion granules that release neuropeptides and hormones into the bloodstream in response to neuronal signals [1]. NE chromaffin cells give rise to adrenal medullary tumors, such as pheochromocytomas or paragangliomas, and, like neuroblasts cells of neuroblastoma (NB), they share a neural crest origin [2]. It was once thought that C cells in medullary thyroid cancer (MTC) also originated from the neural crest. However, recent reports suggest that C cells can be derived from endodermal origin, a theory that remains controversial [3]. This debate can be related to the possibility that C cells underwent a significant lineage shift — between the endoderm and neural crest — during tetrapod evolution.

NETs are rare diseases with an incidence of only about 0.5% of all malignancies, accounting for approximately 2 cases per 100,000 individuals, with a higher prevalence in women under the age of 50 [4]. NETs can occur in endocrine glands such as the thyroid, parathyroid, pituitary, and adrenal medulla or can be dispersed among exocrine cells in the gastrointestinal system, pancreas, lungs, skin, and other tissues [5]. The most frequent locations of NETs are the gastrointestinal tract (62–67%) and the lung (22–27%) [4]. NETs in the adrenal gland and thyroid are much rarer diseases. The incidence of NB is approximately 10.5 cases per million children [6], MTC occurs in about 0.38 cases per million people [7], and pheochromocytoma (PCC) and paraganglioma have an incidence of 2–8 cases per million people [8].

Understanding the cellular mechanisms driving tumorigenesis of NETs is crucial for developing effective therapy. One key aspect of

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tumor cell plasticity and changes in cellular fate that impact tumor development is cell cycle regulation. The cell cycle is a fundamental process that involves DNA duplication and cell division in all mammalian organisms. It consists of four main phases: the first gap phase (G1), DNA synthesis (S), the second gap phase (G2), and mitosis (M). To proceed correctly, cells are equipped with various systems to check for unfavorable conditions, such as DNA damage or a lack of nutrients. Cell cycle checkpoints ensure that progression from one phase to the next occurs normally. There are four major checkpoints: the G1/S checkpoint (restriction checkpoint), the intra-S-phase checkpoint, the G2/M checkpoint, and the M checkpoint (metaphase-to-anaphase transition or spindle checkpoint) [9,10].

The retinoblastoma protein family (pRb), cyclin-dependent kinases (Cdk2, Cdk3, Cdk4, Cdk6), cyclins (cyclin A, cyclin E, D-type cyclins D1-D3), cyclin-kinase inhibitors (INK4 family) are examples of the proteins involved in the cell cycle regulation [11]. DNA replication occurs during the S phase, where the Cyclin D-Cdk4/6 complex, formed in the G1 phase, is crucial for initiating the expression of genes required for S phase progression by phosphorylating Rb protein [12,13]. The Cyclin A-CDK2 complex, which is active during the S phase, drives DNA synthesis. In the G2 phase and at the G2/M transition, the ATR and ATM kinases regulate the activation of the Cyclin B/Cdk1 complex and initiate the repair of damaged DNA [14]. The onset of mitosis, which includes nuclear division, requires the activation of the Cyclin B-CDK1 complex, involving p34 kinase of the CDC2 family, to facilitate progression through the M phase [15].

Cell cycle-related genes play a crucial role in the development and pathogenesis of NETs, influencing tumor growth, differentiation, and response to therapy. Alterations in cell cycle-related gene expression levels and the corresponding inhibition of their encoded proteins can disrupt cell cycle checkpoints, resulting in uncontrolled cell division and promoting the malignant transformation of neuroendocrine cells [16]. For example, deregulation of the cell cycle due to the inhibition of p18, p21, and p27 can be a vital reason for mutations of tumor suppressor gene *MEN1*, leading to the development of parathyroid adenomas, anterior pituitary adenomas, and enteropancreatic NETs [17,18]. However, the cellular diversity within NETs complicates efforts to understand the precise roles and regulatory mechanisms of these genes across cell types, making it harder to understand how cell cycle dysregulation drives NET progression.

Some cell cycle-related genes are overexpressed in cancer cells and promote their uncontrolled proliferation [19], while others are inhibited. Cell cycle-dependent genes and their products could be potential therapeutic targets in the treatment of NETs and other tumors, either as single agents or combined with chemotherapy. Examples include CDK inhibitors, such as flavopiridol (a pan-CDK inhibitor), and selective PKC inhibitors, such as UCN-01 and bryostatin-1 [20,21]. Currently, flavopiridol is under clinical development for cancers such as non-Hodgkin lymphoma and ovarian cancer [22–24], while bryostatin-1 is undergoing trials for pancreatic, lymphoma, and other cancers [25–28]. Approved drugs for NETs include RET inhibitors like selpercatinib and vandetanib for MTC [29, 30], with abemaciclib and palbociclib (CDK 4/6 inhibitors) also in trials for NET and NB treatment [31–33].

The advent of scRNA-seq technology has revolutionized our ability to study cellular heterogeneity and gene expression with exceptional precision. By profiling the transcriptomes of individual cells, scRNA-seq enables the identification of distinct cell clusters within cell types, revealing previously unappreciated heterogeneity in gene expression patterns. This technology allows for the detailed characterization of cell cycle-related gene expression patterns in various cellular contexts, providing valuable insights into the molecular mechanisms underlying NET development and progression.

To comprehensively review cell cycle-related genes identified through scRNA-seq studies, we conducted a systematic literature search using multiple databases, including Web of Science, Scopus, PubMed, and Google Scholar, focusing on all articles published up to August 2024. Our analysis included only those studies that provided clear graphical illustrations of gene expression or explicit mentions of relevant genes in the text. Each identified gene was then independently screened to confirm its connection to cell cycle processes, aiming to create a cohesive synthesis of cell cycle-related findings derived from scRNA-seq research.

2. The key cell cycle-related proteins in tumorigenesis

2.1. Cyclins

Cyclins are a critical family of proteins that function as key regulatory elements in the eukaryotic cell cycle. They are characterized by the presence of a cyclin box, a conserved domain that facilitates binding to CDKs and is essential for their enzymatic activity [34, 35]. Cyclins play pivotal roles in regulating various phases of the cell cycle. Each cyclin-CDK complex is involved in specific transitions: the cyclin D-CDK4/6 complex is crucial for G1 progression, cyclin E-CDK2 facilitates the G1/S transition, and cyclin A-CDK2 promotes DNA synthesis during the S phase. Additionally, cyclin A/B-CDC2 is necessary for the entry into M-phase [34].

The deregulation of cyclin expression is often implicated in cancer. For instance, cyclin D1 is frequently overexpressed in various human tumors, including solid tumors and lymphoid malignancies, due to chromosomal translocations and gene amplification. Cyclin D1 overexpression is linked to poor clinical outcomes, particularly in mantle cell lymphomas, where it is associated with specific chromosomal rearrangements [36]. Similarly, cyclin E's aberrant expression has been connected to oncogenic processes, often resulting from gene amplification and impaired degradation mechanisms. Cyclin E overexpression can lead to decreased cell size and a shortened G1 phase, facilitating uncontrolled cell proliferation [37].

2.2. Cyclin-dependent kinases

CDKs are a family of multifunctional enzymes that modify various protein substrates involved in cell cycle progression and are characterized by their dependence on a regulatory subunit called a cyclin. For their enzymatic activity, CDKs require specific post-translational modifications. Typically inactive on their own, CDKs become activated upon binding to cyclins, which is accompanied

by phosphorylation of a specific threonine residue. This phosphorylation induces a conformational change that enhances the kinase's activity. Once activated, CDKs form cyclin-CDK complexes that phosphorylate specific substrates necessary for advancing the cell cycle. For example, Cdk1 is essential for processes such as centrosome maturation, chromosome condensation, and mitotic entry following nuclear envelope breakdown. The evolutionary expansion of the CDK family in mammals has resulted in the classification of CDKs into three main cell cycle-related subfamilies (Cdk1, Cdk4, and Cdk5) and five transcriptional subfamilies (Cdk7, Cdk8, Cdk9, Cdk11, and Cdk20) [35,36].

Given their central role in cell cycle regulation, CDKs are frequently mutated or deregulated in various diseases, particularly cancer. The CDK-cyclin-Rb pathway is often disrupted during malignant transformation, making CDKs attractive targets for therapeutic intervention. Inhibitors of CDK4 and CDK6, for example, have been designated as breakthrough therapies by the FDA for breast cancer treatment. Furthermore, other CDKs, such as Cdk5 and Cdk8, have been implicated in neurodegenerative diseases and certain cancers, further emphasizing the potential of CDKs as therapeutic targets in oncology and beyond [36,38].

2.3. Cyclin-dependent kinase inhibitors

Cyclin-dependent kinase inhibitors (CKIs) function primarily by interfering with the cyclin-CDK complexes that drive cell cycle progression. CKIs can be classified into several families, each with distinct mechanisms of action. The INK4 family consists of members like $p16^{INK4A}$, $p15^{INK4B}$, $p18^{INK4C}$, and $p19^{INK4D}$. These proteins specifically inhibit CDK4 and CDK6 by preventing their association with cyclin D, thereby disrupting the phosphorylation of the RB protein and blocking cell cycle progression from G1 to S phase. The CIP/KIP family of CDK inhibitors includes three key members: $p21^{CIP1}$, $p27^{KIP1}$, and $p57^{KIP2}$. These proteins primarily inhibit CDKs in the G1 phase of the cell cycle by binding to cyclin–CDK complexes, including cyclin A–CDK2, cyclin E–CDK2, and cyclin D–CDK4/6. In addition to cell cycle regulation, $p21^{CIP1}$ has been shown to perform other cellular functions such as regulating transcription and apoptosis [39,40].

The expression of CKIs is regulated at the transcriptional level by several factors, including oncogenes and tumor suppressor genes. For instance, p21 is transcriptionally activated by the tumor suppressor p53 in response to DNA damage, leading to cell cycle arrest and allowing for DNA repair [41]. On the other hand, the downregulation of CKIs is often seen in various cancers, which contributes to uncontrolled cell cycle progression and tumorigenesis [42,43].

2.4. Checkpoint control proteins

By monitoring cellular conditions and DNA integrity, cell cycle checkpoints maintain genomic stability and prevent the propagation of damaged cells, which is essential for normal cellular function and development [44]. Malfunctions in these regulatory mechanisms can lead to uncontrolled cell proliferation and genomic instability, which are hallmarks of cancer. The p53 protein is a vital tumor suppressor that controls the G1 and G2 checkpoints. It prevents the progression of genetically damaged cells through the cell cycle by binding to DNA and regulating target genes involved in cell cycle arrest and apoptosis. Mutations in the *TP53* gene are prevalent in various cancers, including lung, colon, and breast cancer. Another crucial regulator of the cell cycle is the retinoblastoma protein, which is encoded by the *RB1* gene located on chromosome 13q. pRb regulates the transition from G1 to S phase by binding to E2F transcription factors, which are essential for the expression of genes required for DNA synthesis. When pRb is phosphorylated, it releases E2F, allowing the expression of genes necessary for S phase entry. In its hypophosphorylated state, pRb binds to E2F, inhibiting its activity and preventing the transcription of S phase. Inactivation of *RB1*, due to mutations or dysregulation, can lead to uncontrolled cell proliferation and is implicated in several cancers, such as retinoblastoma and breast cancer [45].

2.5. Transcription factors

Many transcription factors are integral to cell cycle regulation, influencing when cells can grow and divide. For instance, the MycN oncogene is known for its significant roles in promoting cell growth and apoptosis, highlighting the connection between transcription factors and cancer progression [46]. The importance of transcription factors extends into clinical domains, where mutations in these proteins are linked to various diseases, including cancers. Several transcription factors serve as either tumor suppressors or oncogenes, with notable families involved in cancer development including NF-kappaB, AP-1, and the STAT family. Their roles in promoting uncontrolled cell proliferation or inhibiting apoptosis make them critical targets for therapeutic intervention. Researchers are investigating specific inhibitors targeting these transcription factors to develop more effective cancer treatments, making them a focal point in cancer biology [47,48].

2.6. DNA repair proteins

DNA repair proteins are responsible for identifying and rectifying DNA damage, which can occur due to a variety of factors, including environmental stressors and normal metabolic processes. Key DNA repair mechanisms include mismatch repair (MMR), base excision repair (BER), nucleotide excision repair (NER), and homologous recombination (HR). While MMR corrects base mismatches and insertion-deletion loops, and BER addresses small base lesions, NER targets bulky, helix-distorting damage, such as that from UV radiation [49]. Homologous recombination (HR) is particularly vital for repairing double-strand breaks (DSBs), which can be extremely detrimental if not addressed. HR operates mainly during the S and G2 phases of the cell cycle, using a sister chromatid as a template for accurate, error-free repair. This precision is crucial for maintaining genomic stability and preventing tumorigenesis [50,

Table 1
Summary of differentially expressed cell cycle-related genes in neuroblastoma based on scRNA-seq data. Abbreviations: CHCs, chromaffin cells; CPCs, connecting progenitor cells; SCPs, Schwann cell precursors; UCHCs, undifferentiated chromaffin cells; DCHCs, differentiated chromaffin cells. ↑: overexpression; ↓: inhibited expression.

Gene	Functions	Cell type	Expression (↑/↓)	Reference
TOP2A	Chromosome condensation and segregation.	SCPs	↓	Van Haver S. et al. [58]
		Bridge cells	↓	
		CPCs	↓	
		CHCs	↓	
		Prolif. neuroblasts	↑	
		Cycling SCPs	↑	Thirant C. et al. [57]
PCNA	Inducing DNA replication and DNA repair.	Neuroblasts, late neuroblasts, cycling neuroblasts, CHCs, CPCs, cycling SCPs, bridge cells	↑	Thirant C. et al. [57]
CDK4	Progression through the G1 and S/G2 phases.			
E2F1	Progression through the G1/S checkpoint.			
MCM3	Inducing DNA replication.			
CCNB1	Progression through the G2/M checkpoint.	NE malignant cells	↑	Liu Q. et al. [59]
		Cycling SCPs	↑	Thirant C. et al. [57]
		Cycling neuroblasts	↑	
CCNB2	Progression through the Metaphase (spindle) checkpoint.	NE malignant cells	↑	Liu Q. et al. [59]
CCNA2	Activation of Cdk2 during the S phase and Cdk1 during the G2/M transition.			
JUN	Progression through the G1 phase.			
NUF2	CENP-E targeting to kinetochores during mitosis.			
CKAP2	Maintaining centrosome integrity and ensuring proper chromosome segregation.			
CDKN1C	Inducing G1 phase arrest.	Neuroblasts	↑	Thirant C. et al. [57]
		Late neuroblasts	↑	
		CHCs	↑	
		Late CHCs	↑	
		CPCs	↑	
		Bridge cells	↑	
E2F7	Inhibits progression through the G1/S phase.	UCHCs	↑	Dong R. et al. [60]
E2F8				
MYCN	Progression through the G1/S checkpoint.			
EZH2				
CTCF	Chromatin organization during the G1 and G2 phases.			
RAD21	Sister chromatid cohesion from the DNA replication in the S phase to their separation in the M phase.			
HOXC9	Inducing G1 phase arrest.	DCHCs	↑	
FOXD3	Progression through the G2/M checkpoint, and inhibition of transcription during the S phase.	SCPs	↑	Van Haver S. et al. [58]
S100B	Involved in cell cycle arrest, DNA damage control, and pro-apoptotic pathways.			
NR2F2	Progression through the G1/S checkpoint, through the G1 and S/G2 phases.	Bridge cells	↓	
		CPCs and CHCs	↓	
		Neuroblasts	↓	
		Prolif. neuroblasts	↓	
CENPF	Progression through the G2/M checkpoint.	SCPs	↓	
		Bridge cells	↓	
		CPCs	↓	
		CHCs	↓	
		Prolif. neuroblasts	↑	
UBE2C	Transition from mitosis into the G1 phase of the next cell cycle.	NE malignant cells	↑	Liu Q. et al. [59]
		SCPs	↓	Van Haver S. et al. [58]
		Bridge cells	↓	
		CPCs	↓	
		CHCs	↓	
		Prolif. neuroblasts	↑	
EGFR	Progression through the G1/S checkpoint.	Mesenchymal and bridge cell populations	↑	Thirant C. et al. [57]
TNFRSF1A	Inducing either cell proliferation or apoptotic cell death depending on its expression level.			
TIMP3	Maintaining a quiescent state of cells.	Neuroblasts	↑	
		Late neuroblasts	↑	
		CHCs	↑	
		Late CHCs	↑	
		CPCs	↑	
		SCPs	↑	
		Late SCPs	↑	
		Bridge cells	↑	

51].

The DNA damage response involves a complex network of proteins that recognize and repair DNA lesions. Key proteins include ATM and ATR kinases, which are responsible for mediating the repair of DSBs through HR. ATR is particularly crucial for cell survival, while ATM is involved in the phosphorylation of H2AX, facilitating the recruitment of additional repair factors to DSB sites. Failure in these pathways can lead to the accumulation of mutations, driving cancer progression and therapeutic resistance. BRCA1 and BRCA2 are critical tumor suppressor proteins that maintain genomic stability by participating in the homologous recombination repair of DSBs. BRCA2, for example, is essential for the recruitment of Rad51, a protein vital for homologous recombination. Mutations in *BRCA* genes impair DNA repair mechanisms, resulting in increased susceptibility to cancer, particularly breast and ovarian cancers [52–54].

3. Cell cycle-related genes involved in the tumorigenesis of adrenal NETs: neuroblastoma and pheochromocytoma

The adrenal gland NETs are divided into two major types. The first type includes neuroblastic tumors, also named neuroblastoma and ganglioneuroblastoma, which occur in infants and children. The second type is the paraganglioma family, which includes PCC and occurs in adults [55]. To delve deeper into the molecular characteristics of these tumors, scRNA-seq technology has proven invaluable. By profiling individual cells, scRNA-seq enables the identification of distinct cell populations and the analysis of gene expression patterns at unprecedented resolution. To ensure the reliability of scRNA-seq analysis, a sufficient number of cells is essential. 10x Genomics recommends targeting between 500 and 10,000 cells per sample [56]. In our review, the minimum number of cells reported is 3,022 fixed for one sample from the study by Thirant C. et al. [57]. This suggests that every dataset discussed in the review was sufficiently representative to identify key cell clusters.

3.1. Neuroblastoma

In this review, we analyzed four scRNA-seq studies on NB conducted by: Van Haver S. et al. (2023) [58], Thirant C. et al. (2023) [57], Liu Q. et al. (2021) [59], and Dong R. et al. (2020) [60]. A total of 65 tumor samples were collected from 52 patients, along with three samples of peritumoral tissue from three patients, resulting in the isolation of 354,412 cells. Differentially expressed cell cycle-related genes in NB cells are summarized in Table 1, along with their functions as reported in the literature. Fig. 1 illustrates the impact of these genes on the phases of the cell cycle.

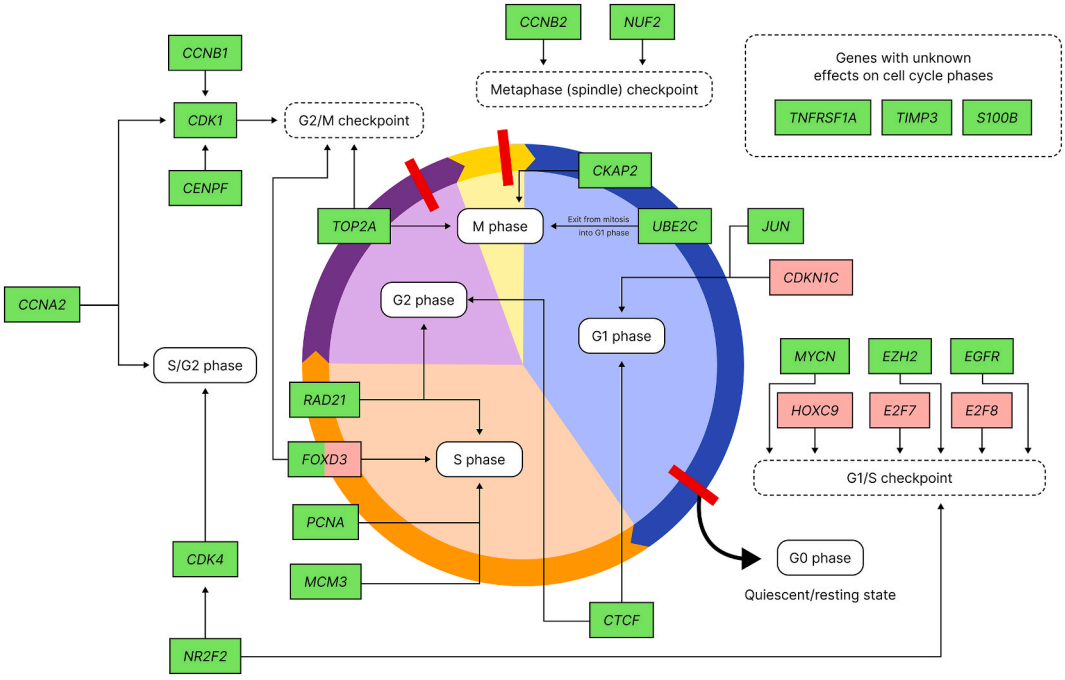

Fig. 1. Differentially expressed cell cycle-related genes in neuroblastoma. *CDK4, CCNA2,* and *NR2F2* promote S/G2 phase progression. *CCNA2, CCNB1, CDK1, CENPF, FOXD3,* and *TOP2A* promote G2/M checkpoint transition. *CTCF* and *RAD21* promote G2 phase progression. *RAD21, PCNA,* and *MCM3* promote the S phase progression, while *FOXD3* inhibits S phase progression. *TOP2A, CKAP2,* and *UBE2C* promote M phase progression. *CCNB2* and *NUF2* promote the spindle checkpoint transition. *CTCF* and *JUN* promote G1 phase progression, while *CDKN1C* promotes G1 phase arrest. *MYCN, EZH2,* and *EGFR* promote G1/S checkpoint progression, while *HOXC9, E2F7,* and *E2F8* block the transition. There are genes with unknown effects on cell cycle phases like *TNFRSF1A, TIMP3,* and *S100B.* The green color represents upregulation and progression of the phase or transition; the red color represents downregulation and cell cycle arrest.

3.1.1. The TOP2A gene expression is elevated in cycling neuroblasts

The *TOP2A (DNA Topoisomerase II Alpha)* gene is highly expressed during mitosis, reaching its peak in the G2-M phase. It plays a crucial role in chromosome condensation and segregation [61]. Compared to normal cells, tumor cells typically have elevated levels of *TOP2A* expression, which aligns with its function in cell cycle progression [62]. Analysis of NB malignant phenotypes using scRNA-seq revealed that *TOP2A* overexpression in NB correlated with the overexpression of *PCNA* and *MKI67* — the well-known proliferation marker presented during all active phases of the cell cycle (G1, S, and M phase) [60,63]. The overexpression of *TOP2A* is tumor cell type-specific as shown by a scRNA-seq study conducted by Van Haver S. et al. In their research, the authors performed scRNA analysis on patient-specific induced pluripotent stem cells (iPSCs) derived from 14 samples from a child with familial NB [58], totaling 49,217 cells. They were able to define five cell types in NB: Schwann cell precursors (SCPs), bridge cells, connecting progenitor cells (CPCs) and chromaffin cells (CHCs), neuroblasts, and proliferating neuroblasts, with a specific overexpression of *TOP2A,* noticed only in proliferating neuroblasts. SCPs, bridge cells, and CPCs are parts of the developmental pathway of chromaffin cells and neuroblasts, which share a common origin, both originating from SCPs [64]. Chromaffin cells, in turn, go through a developmental pathway that includes two intermediate stages: bridge cells and CPCs [65].

In another scRNA-seq study, Thirant C. et al. revealed reversible plasticity between noradrenergic and mesenchymal tumor identities in several NB cell lines and 18 patient biopsies, totaling 54,403 cells [57]. High expression of the *TOP2A* gene was observed primarily in cycling neuroblasts and cycling SCPs, and less with CPCs, late chromaffin cells, chromaffin cells, and bridge cells. Taken together, the studies by Van Haver S. et al. and Thirant C. et al. suggest that *TOP2A* expression is elevated in cycling neuroblasts, indicating a stronger association of this gene with this cell type compared to chromaffin cells or their precursors.

3.1.2. The PCNA gene is involved in the regulation of proliferative activity in chromaffin cells and their precursors

The *PCNA (Proliferating Cell Nuclear Antigen)* gene is necessary for DNA replication and is involved in the RAD6-dependent DNA repair pathway [66]. scRNA-seq analysis showed overexpression of this gene in NB malignant phenotypes [60] and in neuroblasts, CHCs, and CPCs by another study [57], suggesting a role of this gene in the proliferative activity of neuroblastoma cells and cells with NE functions, such as CHCs and their precursors.

3.1.3. Cyclins, cyclin-dependent kinases, and CDK inhibitors: their potential roles in regulating cell fate and differentiation within the NB microenvironment

Cyclins, cyclin-dependent kinases, and CDK inhibitors are integral components of a complex mechanism that regulates cell cycle progression. Cyclins were named for their fluctuating concentrations throughout the various phases of the cell cycle, and numerous cyclin families and subtypes have been identified to date [67]. Cyclins influence cell cycle progression by forming complexes with CDKs and activating the CDK active sites. The scRNA-seq studies highlighted the role of three cyclins: cyclin B1, the product of the *CCNB1* gene, forms with Cdk1 a complex for cell cycle progression through the G2/M checkpoint [68]; cyclin B2, which is involved in the Mad2-associated spindle checkpoint [69]; and cyclin A2 encoded by *CCNA2* gene, which activates Cdk2 during the S phase and Cdk1 during the G2/M transition [70].

Liu Q. et al. performed a scRNA-seq analysis on primary tumors from 17 NB patients and three peritumoral adrenal gland tissues, analyzing a total of 89,882 cells [59]. They identified nine cell types, including neuroendocrine cells, steroidogenic cells, Schwann cells, T cells, B cells, myeloid cells, fibroblasts, ECs, and pericytes. Copy number variation (CNV) analysis identified NE cells as the malignant cells in which 300 meta-genes were preferentially expressed, and data analysis demonstrated high expression of three cyclins, including *CCNB1, CCNB2,* and *CCNA2*. In another scRNA-seq study [57] on mesenchymal and noradrenergic tumor identities, Thirant C. et al. found that *CCNB1* overexpression was associated with cycling SCPs and cycling neuroblasts more than with chromaffin and late chromaffin cells. *CDK4* was shown to be expressed in neuroblasts, CHCs, and CPCs in the NB tumor cells. In the same study, *CDKN1C*, a negative regulator of cell proliferation, exhibited high expression in CPCs. Moreover, *CDK1* was shown to be inhibited in SCPs, bridge, CPCs, and chromaffin cells of NB, and overexpressed in proliferating neuroblasts according to scRNA-seq analysis on patient-derived iPSCs [58].

These findings highlight the complex interplay of cyclins, cyclin-dependent kinases, and their inhibitors in NB development. The observed overexpression of *CCNB1, CCNB2,* and *CCNA2* in NE malignant cells suggests a significant role for these genes in driving tumor cell proliferation. Additionally, the distinct expression patterns of *CDK1, CDK4,* and *CDKN1C* in quiescent and proliferating neuroblasts, chromaffin cells, and their precursors point to their potential roles in regulating cell fate and differentiation within the NB microenvironment.

3.1.4. The E2F family of transcription factors potentially influences the balance between proliferation and differentiation

The E2F family consists of cell cycle activators (E2F1, E2F2, and E2F3a) and DNA-binding repressors (E2F3b and E2F4-8). E2F transcription factors play a crucial role in cell cycle regulation, particularly during the G1/S transition [71]. For example, E2F1 is a cell cycle activator that drives cells through the G1/S checkpoint [72]. *E2F7* expression levels increase as cells enter the S phase; however, when overexpressed, it inhibits S phase entry and cell proliferation [73]. This gene is also involved in the regulation of DNA repair and genomic integrity [74]. E2F8 exhibits a similar effect, as it inhibits E2F1, which promotes G1/S phase progression, and produces cell cycle effects in response to DNA damage [75]. The roles of *E2F1, E2F7,* and *E2F8* genes in the NB microenvironment were elucidated in two scRNA-seq studies.

In the study of Thirant et al., the *E2F1* gene expression was found in the same NB cell clusters as the *PCNA* and *CDK4* genes expression. It was primarily associated with neuroblasts, CHCs, and CPCs of NB [57]. The second scRNA-seq study by Dong R. et al. characterized the malignant phenotypes and developmental trajectories of 16 NB patients, totaling 160,910 cells [60]. A key finding

was the high association of the *E2F7* and *E2F8* genes with undifferentiated chromaffin cells (UCHCs) in NB. The researchers of this study identified nine developing cell types and revealed their corresponding activity in each tumor. They linked 50 signature genes to the differentiation status of CHCs based on their correlation with CHC differentiated scores. The study also suggested that the cycling state of tumor cells upregulates cell cycle-related genes while downregulates genes that promote CHC differentiation, such as *GATA2* and *PHOX2A* genes. These studies revealed that the E2F family members (E2F1, E2F7, E2F8) can play distinct roles in NB development, potentially influencing the balance between proliferation and differentiation.

3.1.5. Other transcription factors and their roles in proliferation and differentiation pathways

NB is a complex malignancy characterized by its heterogeneity and variable clinical outcomes, often linked to the expression of key oncogenes and transcription factors. The role of TF FOXD3 in cell cycle progression in stem cells was elucidated in 2023. Research by Gökbuget et al. demonstrated that the deletion of *FOXD3* in mouse pluripotent stem cells leads to immediate replication stress, the G2/M phase arrest, genome instability, and p53-dependent apoptosis. Additionally, *FOXD3* is known to cause transient inhibition of transcription during the S phase [76], and recent studies have suggested that this gene functions as a tumor suppressor in various types of cancer.

The MycN protein, a product of the *MYCN* proto-oncogene, is involved in multiple signaling pathways that promote cell growth and proliferation in various progenitor cells. The *MYCN* oncogene is strongly linked to a poor prognosis in NB [77,78]. MycN plays a dual role in NB by promoting proliferation in *MYCN*-amplified (MNA) cells while facilitating apoptosis in non-amplified cells. It is known to play a role in the failure of G1 arrest after DNA damage in MNA NB cells, inhibiting p21 induction [79]. Inhibition of *MYCN* in MNA NB cells results in decreased E2F2, Cdk6 mRNA, and ID2 levels while increasing the p27 level, ultimately reducing cells in the S-phase [46]. Conversely, induction of MycN upregulates p53, p21, and Bax protein levels in non-MNA NB cells, pushing these cells toward apoptosis [80].

The *MYCN* and *FOXD3* genes were identified as markers of UCHCs and their precursors in two scRNA-seq studies. In the study by Dong et al., the expression of *MYCN* was closely associated with the undifferentiated proliferative status of tumor (chromaffin) cells in two out of three MNA samples of NB [60]. *FOXD3* was recognized as a marker of SCPs and was found to be overexpressed in the SCP population of NB cells in the iPSC modeling study by Van Haver S. et al. [58].

HOXC9 and JUN are two transcription factors that can underscore the balance between differentiation and proliferation within NB. HOXC9 promotes differentiation and cell cycle arrest in DCHCs, whereas the proto-oncogene JUN drives proliferation in malignant tumor cells [81–83]. In contrast with *MYCN* and *FOXD3, HOXC9* and *JUN* were both highly expressed in differentiated cells within NB in two scRNA-studies. *HOXC9* was highly associated with DCHCs in the study by Dong et al. [60], while *JUN* was preferentially expressed in malignant NE cells in NB in the study by Liu Q. et al. [59].

Known as the vein-specifying transcription factor, NR2F2 directly induces the cell cycle by upregulating various cell cycle-related genes [84]. *NR2F2* demonstrated inhibited expression both in differentiated CHCs, neuroblasts, and their precursors (CPCs and bridge cells) in the iPSC modeling study by Van Haver S. et al. Despite being used as a marker for SCPs, *NR2F2* was not expressed in this cell type [58]. In summary, *NR2F2* was inhibited in all cell types of NB, despite its role in facilitating cell cycle progression. This suggests a potential unknown mechanism of NR2F2 that affects the cell cycle of NB cells.

The interplay of MYCN, HOXC9, JUN, FOXD3, and NR2F2 transcription factors, along with other cell cycle regulators, suggests a delicate balance between proliferation and differentiation pathways in this tumor type. While MYCN, JUN, and NR2F2 promote proliferation, HOXC9 and FOXD3 appear to favor differentiation and cell cycle arrest.

3.1.6. UBE2C is overexpressed in malignant NE cells

The *UBE2C* (*Ubiquitin-conjugating enzyme E2)* gene promotes the degradation of mitotic cyclins A and B, consequently leading to Cdc2 inactivation. This inactivation is essential to transition from mitosis into the G1 phase of the next cell cycle. Additionally, *UBE2C* aids in sister chromatid separation by degrading one or more proteins that play a role in chromatid cohesion [85].

In the scRNA-seq study by Liu Q. et al., the *UBE2C* gene showed high expression in malignant NE cells of NB [59]. Van Haver S. et al. also used *UBE2C* as a proliferation marker in NB cells in their scRNA-seq study. They found that *UBE2C* was inhibited in the SCPs, bridge cells, CPCs, and chromaffin cells of NB while overexpressed in proliferating neuroblasts [58].

3.1.7. Other cell cycle-related genes overexpressed in undifferentiated cells

scRNA-seq studies, discussed in previous sections, have identified additional cell cycle-related genes that are overexpressed in UCHCs. Examples of these genes are *EZH2, CTCF*, and *RAD21*, which were highly associated with UCHCs in NB, as demonstrated in the scRNA-seq study by Dong et al. [60]. Together, these genes regulate cell cycle progression and genomic stability in UCHCs, influencing their proliferative potential and overall tumor dynamics in NB. In addition to their role in regulating the cell cycle in different phases, the *EZH2* gene is also overexpressed in various types of cancer [86–90].

In the scRNA-seq study by Thirant C. et al. [57], *EGFR* and *TNFRSF1A,* which are components of the EGF and TNFα cell signaling pathways, respectively, were found to be preferentially expressed in the mesenchymal and bridge cell populations within the NB IC-pPDXC-63 cell line with noradrenergic to mesenchymal plasticity. This association with mesenchymal tumor identity was also observed in 25 other NB cell lines in the same study. These findings align with the known functions of *EGFR* and *TNFRSF1A* in prompting G1/S phase progression and neural progenitor cell (NPC) proliferation [91–93]. Interestingly, the mesenchymal subpopulation and bridge cells had a higher proportion of cells in the G1 phase, while the noradrenergic population showed a predominance of G2M and S phases.

S100B (S100 calcium-binding protein B), along with *FOXD3,* was identified as a marker of SCPs and was found to be overexpressed in

the SCP population of NB cells in the iPSC modeling study by Van Haver S. et al. [58]. Studies showed that *S100B* upregulates genes involved in cell cycle arrest (*CDKN2A, RB1,* and *RBL2*), DNA damage control (*RAD17*), and pro-apoptotic pathways *(MOAP1)* [94–102].

3.1.8. Other cell cycle-related genes overexpressed in differentiated cells

The previously mentioned scRNA-seq study by Thirant C. et al. also revealed that the *minichromosome maintenance complex component (MCM) 3* and *TIMP3* genes were overexpressed preferentially in differentiated cells (neuroblasts, CHCs, and CPCs) of NBs [57]. It is suggested that *MCM3* can play a role in promoting tumor invasion and metastasis in NB since its overexpression is correlated with poor prognosis in various types of cancer [103–105] and has also been associated with the epithelial-to-mesenchymal transition in human prostate cancer [106]. The results of this study confirm previous findings [107] about the higher expression level of *TIMP3* in slowly dividing compared to rapidly dividing NPCs. The *TIMP3* gene is suggested as a marker of quiescent differentiated noradrenergic cells in NB.

NUF2 and *CKAP2* are examples of the preferentially expressed genes in malignant NE cells, as revealed by Liu Q et al. [59]. Both genes have a role in the mitosis phase of the cell cycle.

Another scRNA-seq study by Van Haver S. et al. suggests that *CENPF* is inhibited in SCPs, bridge, CPCs, and chromaffin cells of NB, but is overexpressed in proliferating neuroblasts [58]. This finding aligns with the known functions of CENP-F (Centromere protein-F), a well-characterized kinetochore protein of the nuclear matrix, that promotes G2/M phase transition through interaction with Cdk1 in HeLa cells [108] and in adrenocortical carcinoma [109].

3.2. Pheochromocytoma

We analyzed two scRNA-seq studies on PCC: Sen Qin et al. (2024) [110] and Xuebin Zhang et al. (2021) [111]. In the study by Sen Qin et al. [110], 11 tissue samples from five patients with PCC were investigated. A total of 133,894 isolated cells were annotated and divided into 67 clusters and 13 cell types. In this review, we will focus on two clusters containing chromaffin cells (the “adrenal cell” cluster and the “proliferating cell” cluster). In the study by Xuebin Zhang et al. [111] three PCCs, including one ectopic case were analyzed. Ectopic adrenocorticotropic hormone (ACTH)- and corticotropin-releasing hormone (CRH)-secreting PCCs are rare tumors that produce ACTH and CRH outside of their normal regulatory sites, resulting in excess cortisol production, and associated with Cushing’s syndrome. In this study, the 44,511 cells were analyzed and grouped into four clusters: ACTH+&CRH+ pheochromocytes, pheochromocytes, adrenocorticals, and sustentacular (supporting) cells. A total of 17 tumor samples were collected from eight patients in these two studies, resulting in the isolation of 178,405 cells.

Differentially expressed cell cycle-related genes in PCC cells are summarized in Table 2, along with their functions as reported in the

Table 2
Summary of differentially expressed cell cycle-related genes in chromaffin cells based on scRNA-seq data. Abbreviations: CHCs, chromaffin cells; ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone. ↑: overexpression; ↓: inhibited expression.

Gene	Functions	Cell type	Expression (↑/↓)	Reference
DLK1	Negative regulator of differentiation, supports the undifferentiated state.	CHCs	↑	Sen Qin. et al. [110], Xuebin Zhang et al. [111]
		ACTH+&CRH+ CHCs	↑	Xuebin Zhang et al. [111]
		Proliferating CHCs	↓	Sen Qin. et al. [110]
RBP1	Downregulation of cell cycle progression and G1/S phase arrest.	CHCs	↑	Sen Qin. et al. [110]
		Proliferating CHCs	↓	
GNAS	Progression through the G1/S checkpoint.	CHCs	↑	Xuebin Zhang et al. [111]
		ACTH+&CRH+ CHCs	↑	
UCHL1	Induces cell cycle arrest in the G0/G1 phases.	CHCs	↑	
		ACTH+&CRH+ CHCs	↑	
RGS5	Involves in mechanisms of early cell cycle entry.	CHCs	↑	
RGS4	Induces G2/M phase cell cycle arrest and prometaphase block.	CHCs	↑	Sen Qin. et al. [110]
STC1	Regulates calcium homeostasis and is involved in proliferation, differentiation, and apoptosis.			
PFKP	Glycolysis and cell cycle progression.			
CALM2	Progression through the G1/S checkpoint.			
STMN1	Formation and reorganization of the cytoskeleton as well as progression through the G2/M checkpoint.			
DIRAS3	Downregulates cell cycle progression and induces the G1/S phase arrest.	ACTH+&CRH+ CHCs	↑	Xuebin Zhang et al. [111]
POMC	Progression of the G1 phase and the initiation of DNA synthesis.			
CRH	Affecting cell proliferation, apoptosis, and stress responses.			
TOP2A	Chromosome condensation and segregation.	Proliferating CHCs	↑	
MKI67	Chromosome segregation and nuclear division.			

literature. Fig. 2 illustrates the impact of these genes on cell cycle phases.

3.2.1. The role of overexpressed genes in proliferation and differentiation of chromaffin cells

Both scRNA-seq studies demonstrated a strong association between *DLK1* (*Delta Like Non-Canonical Notch Ligand 1*) gene expression and adrenal-derived neoplasm tumorigenesis. While the study by Xuebin Zhang et al. [111] revealed a consistent *DLK1* overexpression pattern across all PCC cell clusters, the study by Sen Qin et al. [110] further validated it, along with revealing *RBP1 (Retinol Binding Protein 1)* accelerated cell cycle at the G1 phase, as a specific marker for adrenal cells. *DLK1* is involved in cell differentiation and proliferation, especially in stem and progenitor cells and acts as a negative regulator of differentiation, maintaining an undifferentiated state of stem and progenitor cells [112]. *DLK1* knockout weakens Notch signaling, impairs stem cell function, increases mitochondrial activity, and triggers division in quiescent stem cells [113–115]. *RBP1*, a gene essential for retinol homeostasis, was overexpressed in PCCs but downregulated in most cancers, including ovarian [116] and breast cancer [117]. It is suggested that *RBP1* plays a crucial role in regulating cell growth and differentiation, inducing cell cycle arrest in the G1 phase [118]. In breast cancer, lower *RBP1* expression correlates with increased proliferation. Overexpressing *RBP1* in PCC tumor cells can inhibit proliferation, suggesting its unique mechanism in PCC that affects the cell cycle.

The *GNAS (Guanine Nucleotide binding protein, Alpha Stimulating activity polypeptide)* gene encodes the alpha subunit of a G protein and was overexpressed in most chromaffin cells of PCC [111]. A recent study investigated the impact of *GNAS* expression on the proliferation and migration of breast cancer cells. Elevated *GNAS* expression was associated with increased proliferative activity due to cyclin D1 and Cdk4 expression and G1/S checkpoint transition [119].

The gene *UCHL1 (Ubiquitin C-Terminal Hydrolase* L*1*) was overexpressed in pheochromocytes and described as both an oncogene [120] in multiple melanoma and a tumor suppressor [121] in breast cancer. *UCHL1* overexpression suppresses the growth of breast cancer tumor cells by inducing G0/G1 arrest and apoptosis via disruption of p53 signaling. On the other hand, *UCHL1* can interact with the PI3K/Akt signaling pathway, which regulates cell proliferation, influencing cell growth and survival in multiple myeloma cells. The first insight is that the *UCHL1* gene can promote cell cycle progression due to its overexpression in PCC, but more studies are needed to elucidate the distinct role of this gene in PCC.

RGS5 (Regulator of G Protein Signaling 5), a regulator of G-protein signaling, is overexpressed in various cancers [122–124], including PCC [111]. Studies have shown that *RGS5* expression is correlated with cell proliferation in various cell types. For example, reducing *RGS5* levels in ovarian carcinoma cells after mitogenic stimulation inhibited their growth by arresting the cell cycle at the G1 phase. Similarly, the reconstruction of *RGS5* expression level in vascular smooth muscle cells (SMCs) led to the downregulation of cyclin D, Cdk1, and PCNA preventing cell G0/G1 transition in proliferating SMCs.

3.2.2. Overexpressed cell cycle-related genes in tumor-associated chromaffin cells

In the study by Sen Qin et al. [110] the heterogeneity of PCC was examined, revealing two distinct clusters of chromaffin cells (A and B), each suggesting unique biological characteristics. Gene expression profiling differentiated these clusters based on their

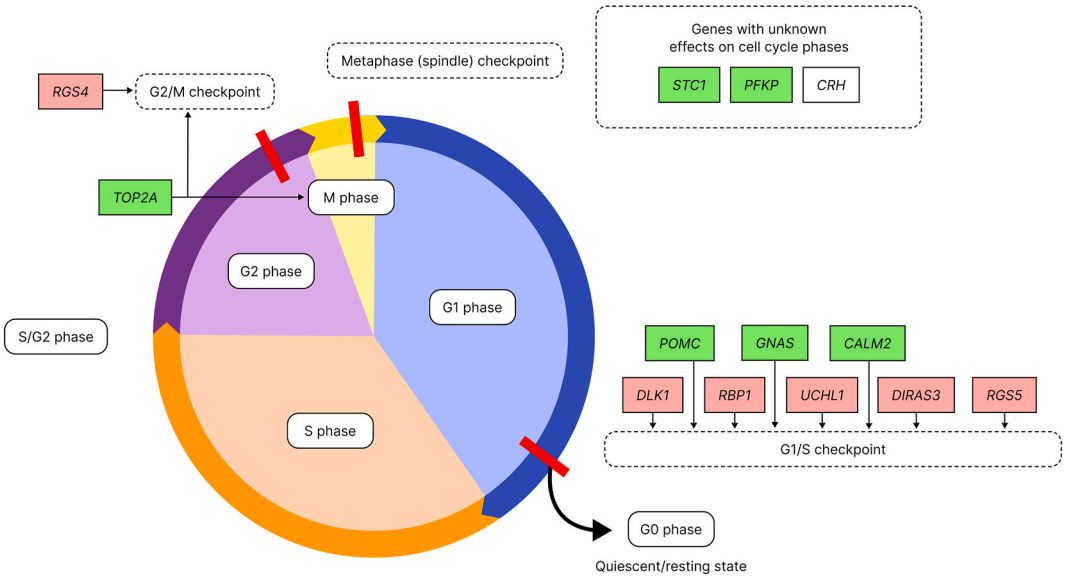

Fig. 2. Differentially expressed cell cycle-related genes in pheochromocytoma and their role in the cell cycle regulation. *TOP2A* promotes G2/M checkpoint transition and M phase progression, while *RGS4* induces G2/M checkpoint failure. *POMC, TMEM176A, GNAS* and *CALM2* promote G1/S checkpoint transition, while *DLK1, RBP1, UCHL1, DIRAS3,* and *RGS5* block it. There are genes with unknown functions on cell cycle phases: *TMEM176B, STC1, PFKP,* and *CRH.* The green color represents upregulation and progression of the phase or transition; the red color represents downregulation and cell cycle arrest.

metabolic and NE phenotypes. Cluster A was characterized by an enrichment of genes related to energy metabolism such as *RGS4, STC1,* and *PFKP*. In contrast, cluster B exhibited an enrichment of genes involved in NE functions, including *CALM2, EIF4A2,* and *STMN1*.

The *RGS4* gene, like *RGS5*, plays a role in regulating the cell cycle by negatively modulating G protein activity, promoting cell cycle arrest at the G2/M phase accompanied by increased phosphorylation of Cdc2 and Cdc25C in MDA-MB-231 and MCF-7 cell lines of breast cancer [125]. *STC1 (Stanniocalcin 1)* plays a dual role in cancer progression by promoting cell cycle transition and regulating apoptosis through various signaling pathways. Elevated *STC1* expression has been linked to several cancers, including PCC, thyroid cancer, glioblastoma, prostate cancer, and cervical cancer [126–129]. *STC1*'s modulation of key pathways, including TGF-β/SMAD4, NF-κB, and JNK/c-Jun, supports tumor growth, cell survival, and metastasis, making it an important factor in cancer progression [129]. *PFKP (Phosphofructokinase, Platelet)* encodes phosphofructokinase, a key glycolytic enzyme. While the precise role of phosphofructokinase in cell cycle regulation is not fully elucidated, its enzymatic activity strongly correlates with cellular energy balance, which impacts cell cycle progression. Some studies have demonstrated that *PFKP* is overexpressed in PCC, colorectal [130] and lung cancer [131] and promotes G1, S, and G2/M phase progression.

As for the cluster B and its genes, *CALM2 (Calmodulin 2)* encodes the Calmodulin 2 binding protein, which interacts with Ca2+/calmodulin-dependent protein kinases and cyclins, playing key roles in cell proliferation, apoptosis, and tumor progression. Studies have consistently demonstrated the overexpression of *CALM2* in various cancers, including PCC, hepatocellular carcinoma (HCC) [132], breast cancer [133], and gastric cancer [134,135], highlighting its role in chemoresistance. In gastric cancer, *CALM2* confers resistance to tyrosine kinase inhibitor afatinib by downregulating Akt signaling and activating the mitochondrial apoptotic pathway. Studies on HCC cells have identified E2F5 as a key downstream target of *CALM2*. *STMN1 (Stathmin 1)* is a gene encoding protein Stathmin 1, a cytosolic protein that plays a crucial role in regulating microtubule dynamics, which in turn directly influences the cell cycle progression. Overexpression of *STMN1* has been frequently observed in various tumor types, including PCC, adrenocortical, lung, and esophageal carcinomas [136,137], promoting proliferation, invasion, and metastasis.

3.2.3. *Genes overexpressed in chromaffin cells of ectopic ACTH and CRH-secreting PCC*

The study by Xuebin Zhang et al. [111] identified a multifunctional chromaffin-like cell type in ACTH/CRH-secreting pheochromocytomas characterized by high expression of both *POMC* (the precursor of ACTH) and *CRH*, termed ACTH+ and CRH+

Table 3
Summary of differentially expressed cell cycle-related genes in C cells based on scRNA-seq data. ↑: overexpression; ↓: inhibited expression.

Gene	Functions	Cell type	Expression (↑/↓)	Reference
AIMP1	Negative regulation of the TGF-β signaling pathway (prevention of G1 phase arrest and promotion of cell growth).	Malignant C cells	↑	Chen D. et al. [148]
CDH1	Induces G1 phase and G2/M phase arrest.		↑	
GPI	Proliferation and motility of cancer cells. Progression through the G2/M phase.		↑	
HLA-E	Promotion of the senescent state of cells.		↓	
ARF1	Incomplete chromosome segregation and errors in furrow ingression.		↓	
COPA	The exact functions remain unknown.		↓	
SDHA	Inhibits cell proliferation, while improving the ability to survive and form colonies.	C cells (early phase of tumor transformation)	↓	Wang Lf. et al. [149]
		C cells (early cancerous cell population)	↓	
		Adult malignant C cells	↑	
PGK1	Progression through the G1/S checkpoint.	C cells (early phase of tumor transformation)	↓	
		Adult malignant C cells	↑	
EPCAM	Promotes transition from G1 phase to S phase by influencing cyclin D1.	C cells (early phase of tumor transformation)	↑	
PROM1	Increases proliferation of stem cells.			
MAP3K4	Functions as both a tumor promoter and suppressor, being activated by a variety of factors.			
PPIH	Associated with DNA repair, G2/M checkpoint, and DNA replication.	Adult malignant C cells	↑	
RICTOR	Progression through the G1/S checkpoint.	C cells (early phase of tumor transformation)	↓	
		Adult malignant C cells	↑	
BCL2	Inhibits apoptosis and G1/S checkpoint transition. Delays E2F1 accumulation during G1 progression.	C cells (early phase of tumor transformation)	↓	
		Adult malignant C cells	↑	
CEACAM5	Maintains the proliferative potential of adult cells while promoting the quiescent state of stem cells.	C cells (early phase of tumor transformation)	↓	
		Adult malignant C cells	↑	
RET	Promotes transition from G1 phase to S phase.	C cells (early phase of tumor transformation)	↓	
		C cells (early cancerous cell population)	↓	
		Adult malignant C cells	↑	

pheochromocytes. Here, we will analyze the genes that were specifically overexpressed in this unique cell cluster.

Many PCCs arise from hereditary mutations in proto-oncogenes or tumor suppressor genes. The *DIRAS3 (DIRAS Family GTPase 3)* gene, also known as *ARHI,* encodes a tumor suppressor protein that inhibits the RAS oncogene. Increased expression of *DIRAS3* has been observed in several types of tumors, including sporadic PCCs [138]. It is noteworthy that *DIRAS3* expression was detected exclusively in the ACTH+&CRH+ pheochromocyte cluster, suggesting a potential role for this gene in the pathogenesis of this specific tumor subtype. In primary human pheochromocytoma cells with *DIRAS3* overexpression cyclin D1 and cyclin E were significantly reduced, confirming the cell cycle arrest at the G1/S stage [138]. The mechanisms underlying this regulation of the cell cycle influence the expression of key regulatory proteins in the G1 phase, including Cdk2, Cdk4/6, $p21^{WAF1}$, and $p27^{Kip1}$, as well as cyclins E, A, and D1 [139,140].

Another gene that has been overexpressed only in ectopic PCCs chromaffin cells [141] is *POMC (Proopiomelanocortin)*. *POMC* encodes a preproprotein that is a precursor to ACTH and N-terminal peptides (N-POMC). The role of ACTH in the cell cycle is actively researched, as it is involved in G1 phase progression and the initiation of DNA synthesis. ACTH promotes proliferation by activating the ERK-MAPK pathway [142]. Since tumor cells often exhibit disruption in the transition from G1 to S phase, studying the expression of the *POMC* gene, which can influence this process, is highly relevant [143].

CRH was overexpressed only in a cluster of ACTH+&CRH+ pheochromocytes. While this gene is traditionally associated with the endocrine system and stress response, recent studies have implicated *CRH* in several carcinomas, including breast [144], ovarian [145], and endometrial [146] carcinomas as well as in PCC tumorigenesis. CRH binds to specific receptors on PCC cells, activating intracellular signaling pathways that promote cell proliferation and inhibit apoptosis, thereby contributing to tumor growth.

3.2.4. Genes overexpressed in proliferating chromaffin cells

In the study by Sen Qin et al. [110], it was demonstrated that the *MKI67* and *TOP2A* genes were exclusively overexpressed in the chromaffin proliferating cell cluster. As mentioned earlier, the *TOP2A* gene encodes a DNA topoisomerase that regulates DNA topology during transcription and replication, playing a key role in chromosome aggregation. Overexpression of this gene has been found in various tumors, such as NB (see section 3.1.1), and it correlates with enhanced metastasis and poor disease prognosis. In the study by Solhusløkk Höse et al. [147], *TOP2A* overexpression in PCC was investigated as a marker of poor clinical outcomes, correlating with high metastasis potential and contributing to carcinogenesis.

4. Cell cycle-related genes influence the tumorigenesis of medullary thyroid cancer

Differentially expressed cell cycle-related genes in MTC cells are summarized in Table 3, along with their functions as reported in the literature. Fig. 3 illustrates the impact of these genes on the phases of the cell cycle.

Currently, only two scRNA-seq studies investigating the NET in the thyroid gland have been published and conducted by Chen D.

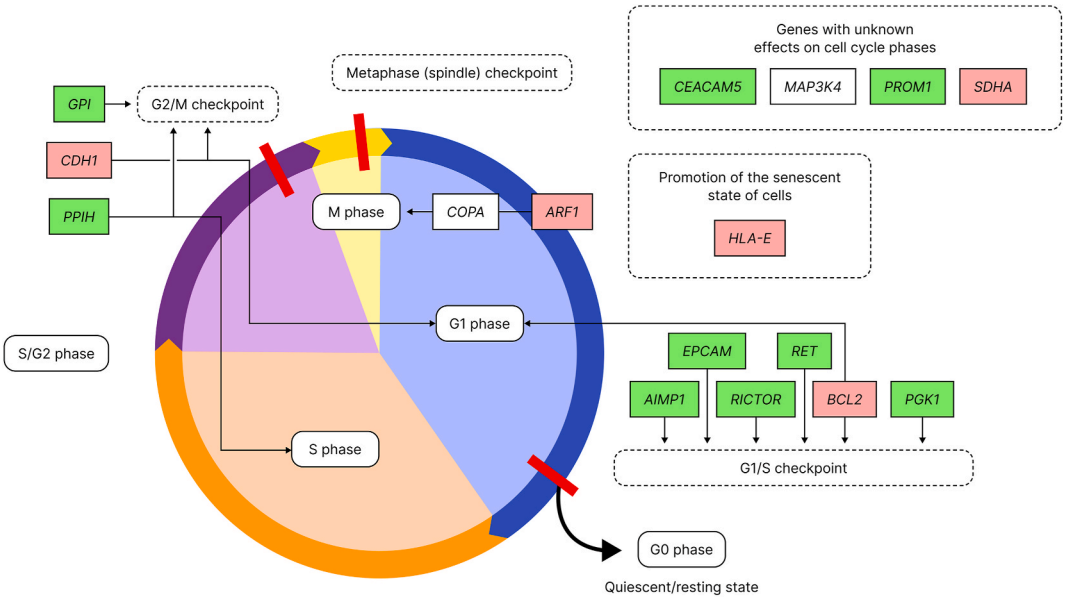

Fig. 3. Differentially expressed cell cycle-related genes in MTC. *GPI* and *PPIH* promote G2/M checkpoint transition, while *CDH1* blocks the transition. *PPIH* promotes S phase progression. *ARF1* inhibits M phase progression through the *COPA* gene interaction. *CDH1* promotes G1 phase arrest. *AIMP*, *EPCAM, RICTOR, RET,* and *PGK1* genes promote G1/S checkpoint progression. *BCL2* inhibits G1/S checkpoint transition and blocks G1 phase progression. *HLA-E* promotes the senescent state of cells. There are genes with unknown effects on cell cycle phases like *CEACAM5, MAP3K4, PROM1,* and *SDHA.* The green color represents upregulation and progression of the phase or transition; the red color represents downregulation and cell cycle arrest.

et al. [148] and Wang Lf. et al. [149]. In the first study by Chen D. et al., the researchers performed single-cell transcriptome sequencing on two samples from the primary tumor and metastatic lymph nodes of one patient, totaling 12,830 cells. The researchers identified six main cell clusters: C cells, T cells, B cells, fibroblasts, endothelial cells, and myeloid cells. Notably, the C cell cluster was characterized as a malignant cell cluster. The results of the study by Chen D. et al. showed that six cell cycle-related genes were differentially expressed in the C cells of MTC. Three of these genes were overexpressed *(AIMP1, CDH1,* and *GPI),* while the other three were inhibited *(HLA-E, ARF1,* and *COPA)*.

The second scRNA-seq study conducted by Wang Lf. et al. obtained a total of 32,544 cells from tumor samples of three patients with MTC. The researchers identified seven distinct cell types: thyroid parafollicular cells (C cells), smooth muscle cells, fibroblasts, endothelial cells, dendritic cells, T cells, and neutrophils. They further divided the C cell cluster into seven subclusters, labeled C0 through C6. Through CNV analysis, subclusters C2 and C4 were identified as non-tumor cells, while the other subclusters were classified as tumor cells. Additionally, using time-series trajectory analysis, the researchers proposed that the C2 subcluster represents an early phase of tumor transformation, which progresses to C3, an early cancerous cell population. The subsequent steps in the transformation involve malignant cell subpopulations C0, C1, C5, and C6.

4.1. Genes overexpressed in early- and late-developed C cells

The known role of *AIMP1* in the cell cycle is to prevent G1 phase arrest and prompt cell growth via negative regulation of the TGF-β signaling pathway [150–152]. This explains its overexpression in approximately 35% of the C cells in MTC in the study by Chen D. et al. Similarly, *Glucose-6-phosphate isomerase (GPI),* which is involved in the interconversion of glucose-6-phosphate and fructose-6-phosphate, was overexpressed in about 25% of C cells. This is expected due to its previously described role as a prognostic biomarker in various types of cancer and as a promoter of the cell cycle progression through the G2/M phase in lung adenocarcinoma [153–158]. The *Succinate Dehydrogenase (SDHA)* and *Phosphoglycerate kinase 1* (*PGK1)* genes, which were differentially expressed in C cells according to the scRNA-seq study by Wang et al., are also significant for metabolic regulation, similar to *GPI.* These genes were inhibited in the early phase of tumor transformation but were overexpressed in late-developed malignant cell populations. This finding aligns with previous studies: *PGK1* is known to promote tumor cell proliferation [159,160], while *SDHA,* although it acts as an inhibitor of cell proliferation, enhances the ability of cancer cells to survive and form colonies [161].

Cadherin-1, also known as E-cadherin, is encoded by the *CDH1* gene and is a member of the cadherin superfamily. The results showed that *CDH1* was overexpressed in approximately 25% of the C cells in MTC in the study by Chen D. et al. E-cadherin leads to a significant reduction in DNA synthesis and blocks cell cycle progression in the G1 phase [162]. Furthermore, a study by Gharbi S. et al. found that at least one miRNA targeting the *CDH1* gene promotes cell cycle arrest at the G2/M phase and has a tumor suppressor effect due to the upregulation of *PTEN* [163]. Thus, the role of *CDH1* in MTC C cells remains unclear, given its tumor suppressor and cell cycle arrest effects on one hand, and its overexpression in the cluster of C cells on the other.

In the study by Wang Lf. et al., three genes were found to be overexpressed primarily in the early phase of C cell transformation, with their expression levels decreasing as the tumor progressed. The *EPCAM* and *PROM1* genes are recognized as progenitor cell markers. The *EPCAM* gene encodes the Epithelial Cell Adhesion Molecule, which is frequently overexpressed in embryonic stem cells, cancer-initiating cells, and other progenitor populations [164]. Prominin 1, the product of the *PROM1* gene, serves as an upstream activator of the PI3K/Akt pathway and is associated with the proliferation of stem cells [165,166]. The *MAP3K4* gene exhibits a dual role as both a tumor promoter and suppressor, depending on the tumor type and its various downstream pathways [167]. In the study by Wang, Lf. et al., it appears that *MAP3K4* also plays a significant role in cell cycle progression within tumor progenitor cells.

In the same study, the genes *PPIH, RICTOR, BCL2, CEACAM5,* and *RET* were found to be overexpressed in subclusters of late-developed tumor C cells. *BCL2* is a well-known oncogene and regulator of apoptosis, and it also acts as an antiproliferative factor. It enhances the G0 phase and delays the transition from G0 to S phase by preventing the accumulation of E2F1 during the G1 phase. The genes *PPIH, RICTOR,* and *CEACAM5* contribute to the proliferative potential of cells. For instance, PPIH (Peptidylprolyl Isomerase H) levels are markedly elevated in liver hepatocellular carcinoma, colon adenocarcinoma, and breast cancer, and this overexpression is associated with a poorer prognosis in these cancers [168]. RICTOR is one of the core subunits of the mTORC2 complex [169]; its knockdown has been shown to attenuate cell cycle progression and enhance apoptosis in various cancer types [170–173]. *Carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5),* also known as *CD66e,* is a member of the carcinoembryonic antigen (CEA) gene family. *CEACAM5* plays a role in maintaining the proliferative potential of cells and is recognized as a biomarker for several malignancies, including melanoma, lung, colorectal, and pancreatic cancers [174,175]. Notably, in the study by Ma K. et al. [176], *CEACAM5* expression was also associated with the quiescence of hematopoietic stem cells, which aligns with the observed inhibited expression of this gene in the progenitor tumor cell subcluster in the scRNA-seq study by Wang Lf. et al.

The *RET* proto-oncogene is associated with the development of various types of cancer, including MTC and PCC, which can occur together in MEN2A or MEN2B syndromes [177]. Disruption of RET signaling in MTC, as reported in the study by Drosten M. et al. [178], led to reduced cell cycle progression and was associated with a loss of the neoplastic phenotype. This finding aligns with those of Wang Lf. et al., where *RET* gene expression was inhibited in normal C cells and during the early phase of C cell transformation, but was promoted in late-developed tumor C cells.

4.2. Genes with inhibited expression in C cells

HLA-E, which encodes a non-classical major histocompatibility complex class I antigen [179], has been inhibited in approximately 50% of the tumor cells in MTC in the study by Chen D. et al. This finding is consistent with other previous studies of this gene. In the

transcriptomic study of replicative senescent human fibroblasts by Lackner D. et al. in 2014 [180], *HLA-E* was overexpressed more than twofold compared to proliferative cells. This observation was further supported by Pereira B. et al. in their 2019 study [181], which revealed that *HLA-E* expression is increased in senescent cells. Moreover, despite the previously described overexpression of *ARF1* in breast, ovarian, and prostate cancers [182–184], it was inhibited in about 50% of the C cells in MTC, suggesting unique mechanisms of cell cycle regulation in this rare thyroid malignancy.

COPA is a coat subunit α of Golgi-derived non-clathrin-coated vesicles. It is a coatomer or coat protein complex I component [185, 186]. Similar to its regulator *ARF1, COPA* was inhibited in the C cells in the same study, although the percentage of expressing cells was lower, at around 15–20%. Song Y. et al. have reported that *COPA* can be differentially edited in HCC [187]. One of the *COPA* variants ($COPA^{I164V}$) appears to act as a tumor suppressor, while the wild-type form promotes cancer cell growth [188]. While the exact functions of *COPA* in the cell cycle remain unknown, it is unclear whether its inhibition was connected to the inhibition of *ARF1* or involved other mechanisms.

5. Limitations

Only a limited number of scRNA-seq studies have focused on NETs of the adrenal and thyroid glands. The limitations of this review stem from the rarity of these neoplasms and the novelty of the scRNA-seq technology. This need for more research can impede a comprehensive understanding of cell cycle dynamics and the associated pathways in these tumors. Nevertheless, this review aims to stimulate further investigations into the functions of cell cycle-related genes in NETs. A deeper understanding of these mechanisms is essential for elucidating the actual pathogenesis of these tumors.

6. Future prospect

Investigating cell cycle-related genes facilitates the identification of potential biomarkers for tumor aggressiveness and behavior. The development of a gene panel represents a significant outcome of this research, aimed at improving the diagnostic and prognostic capabilities for NETs in the adrenal and thyroid glands. Additionally, these molecular targets open new avenues for the development of targeted therapies, which is particularly relevant in the context of cancer resistance to traditional treatment methods.

In our review, we identified and categorized approved drugs targeting cell cycle-related proteins, which are encoded by genes highlighted above (Table 4). Additionally, we included drugs currently undergoing clinical research (Table 5). Some of these drugs are indicated for the types of cancer discussed in our review. For instance, Pralsetinib, Selpercatinib, and Vandetanib are approved therapies for MTC that target the RET protein. In the realm of clinical trials, promising candidates such as SY-5007, TY-1091, and LOXO-260 are also designed to target RET in patients diagnosed with MTC. Furthermore, the FDA-approved Sunitinib Malate and the investigational drug ADCT-701, both targeting DLK1, are applicable for NETs. Another noteworthy compounds, CID-078, which inhibits Cyclin B1 and Cyclin A, and the EZH2 inhibitors Igermetostat and Mevrometostat are currently in clinical trials for NET

Table 4
Summary of approved drugs targeting cell cycle-related proteins. Abbreviations: BC, breast cancer; SCLC, small cell lung cancer; TC, testicular cancer; ML, myelogenous leukemia; ALL, acute lymphoblastic leukemia; ES, epithelioid sarcoma; FL, follicular lymphoma; GST, gastrointestinal stromal tumor; RCC, renal cell carcinoma; CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma; NSCLC, non–small cell lung cancer; HCC, hepatocellular carcinoma; DTC, differentiated thyroid cancer; EC, endometrial carcinoma.

Target protein	Type of drug	Name of drug	Type of cancer	Reference
TOP2A	TOP2A inhibitor	Doxorubicin	BC	[189]
		Epirubicin	BC	[190]
		Etoposide	SSLC, TC	[191]
		Mitoxantrone	ML	[192]
		Teniposide	ALL	[193]
CDK4/6	CDK4/6 inhibitor	Palbociclib, ribociclib, abemaciclib	BC	[194]
EZH2	EZH2 inhibitor	Tazemetostat	ES, FL	[195, 196]
EGFR	EGFR inhibitor	Lapatinib Ditosylate	BC	[197]
DLK1	Multi-kinase inhibitor	Sunitinib Malate	GST, RCC, pancreatic NETs	[198]
EpCAM	CD3/EpCAM bispecific monoclonal antibody	Catumaxomab	EpCAM-positive carcinomas	[199]
BCL-2	Microtubule inhibitor	Ixabepilone	BC	[200]
	BCL-2 inhibitor	Venetoclax	CLL, SLL, ALL	[201]
RET	RET inhibitor	Pralserinib	RET fusion–positive NSCLC, RET fusion–positive thyroid cancer	[202]
		Ponatinib	ALL, ML	[203]
		Selpercatinib	RET fusion–positive NSCLC, MTC with a RET mutation, thyroid cancer with a RET gene fusion, solid tumors with a RET gene fusion	[29]
	Multi-kinase inhibitor	Cabozantinib	RCC, HCC	[204]
		Lenvatinib	DTC, RCC, HCC, EC	[205]
		Sorafenib	HCC, RCC, DTC	[206]
		Vandetanib	MTC	[30]

Table 5
Summary of drugs targeting cell cycle-related proteins and undergoing clinical research. Abbreviations: OS, osteosarcoma; LMS, leiomyosarcoma; SS, synovial sarcoma; OC, ovarian cancer; NSCLC, non-small cell lung cancer; PANC, pancreatic cancer; BC, breast cancer; LC, lung cancer; SCLC, small cell lung cancer; SC, stomach cancer; BCa, bladder cancer; EC, esophageal carcinoma; HNSCC, head and neck squamous cell carcinoma; UC, urothelial carcinoma; PC, prostate cancer; CC, cervical cancer; ECa, endometrial cancer; AST, advanced solid tumor; CRC, colorectal cancer; DTC, differential thyroid cancer; MM, multiple myeloma; PDAC, pancreatic ductal adenocarcinoma; PTC, papillary thyroid cancer.

Target protein	Type of drug	Name of drug	Type of cancer	Phase	Reference
PCNA	PCNA inhibitor	AOH1996	OS, LMS, SS, OC, NSCLC, PANC	Phase I	[207]
Cyclin B1	Cyclin B1 inhibitor	Cyclin B1/WT-1/CEF (antigen)-loaded DC vaccination combined with preoperative chemotherapy	BC	Phase II	[208]
Cyclin B1 and Cyclin A	Cyclin B1 and Cyclin A inhibitor	CID-078	LC, NET, BC, SCLC, NSCLC, PANC, SC	Phase I	[209]
NUF2	NUF2 inhibitor	DURvalumab in combination with S-488210/S-488211	BCa	Phase Ib/II	[210]
		S-588210 (S-488210+S-488211)	LC, EC, mesothelioma, BCa	Phase I	[211]
EZH2	EZH2 inhibitor	Igermetostat (in combination with pembrolizumab)	HNSCC, UC, PC, SCLC, NSCLC, CC	Phase Ib/II	[212]
		Mevrometostat	PC, SCLC, FL	Phase I	[213]
TNFRSF1A (TNFR1)	Viral-based cancer therapy with TNFRSF1A transgene	Ofranergene obadenovec (in combination with Bevacizumab)	Glioblastoma	Phase III	[214]
		Ofranergene obadenovec (in combination with Paclitaxel)	OC	Phase III	[215]
		Ofranergene obadenovec (in combination with Nivolumab)	CRC	Phase II	[216]
		Ofranergene obadenovec	DTC	Phase II	[217]
DLK1	Anti-DLK1 Monoclonal Antibody	ADCT-701	NET	Phase I	[218]
STMN1	Bifunctional short hairpin RNAs (shRNA) against human stathmin 1 (STMN1)	pbi-shRNA STMN1 Lipoplex	Advanced cancer	Phase I	[219]
HLA-E	CRISPR-Edited Allogeneic Anti-BCMA CAR-T Cell Therapy (insertion of a B2M-HLA-E-peptide fusion protein transgene)	CB-011	MM	Phase I	[220]
	Allogeneic anti-CD19 CAR T cells (with HLA-E transgene)	PBCAR-19B(Baxalta/Precision BioSciences)	CD19-expressing malignancies	Phase I	[221]
CEACAM5	Antibody–drug conjugate targeting CEACAM5	Tusamitamab ravtansine	CEACAM5-positive NSCLC	Phase III	[222]
			BC, PANC	Phase II	[223]
	Autologous anti-CEA logic-gated CAR T cells	A2B-530	CRC, PANC, NSCLC, and other solid tumors that express CEA and have lost HLA-A*02 expression	Phase I/II	[224]
	CEACAM5/4-1BB bispecific agonist antibody	LM-24C5	AST	Phase I/II	[225]
	Anti-tumor-associated CEACAM-5/6 monoclonal antibody	NEO-201	NSCLC, HNSCC, CC, UC, ECa	Phase I/II	[226, 227]
	Anti-CEACAM5 CAR-T	Anti-CEACAM5 CAR-T	CRC with liver metastases	Phase I	[228]
	4-1BB/CEACAM5 bispecific antibody	BGB-B167	AST	Phase I	[229]
	Antibody–drug conjugate targeting CEACAM5	Precemtabart tocentecan	CRC	Phase I	[230]
	Antibody–drug conjugate targeting CEACAM5	SGN-CEACAM5C	Colorectal neoplasms, NSCLC, stomach neoplasms, PDAC	Phase I	[231]
RET	RET Inhibitor	SY-5007	RET fusion-positive NSCLC, RET fusion-positive MTC	Phase I/II	[232]
		TY-1091	RET fusion-positive NSCLC, RET fusion-positive MTC, RET-altered PTC	Phase I/II	[233]
		LOXO-260	RET fusion-positive NSCLC, RET fusion-positive MTC	Phase I	[234]

treatment. There are additional targets, such as MycN, CENPF, Ki-67, CDH1, ARF1, and PGK1, that are in preclinical stages. While we must await further results to assess their potential, there are promising developments in this area.

Fig. 4 illustrates the complex interplay between cell cycle-related genes and their influence on various signaling pathways in NETs, which are associated with the cell cycle. A deeper understanding of these intricate molecular networks may unveil novel therapeutic targets and strategies. By integrating transcriptomic and proteomic analyses with functional studies, researchers can identify key regulatory nodes and develop targeted interventions to disrupt NET tumorigenesis and progression.

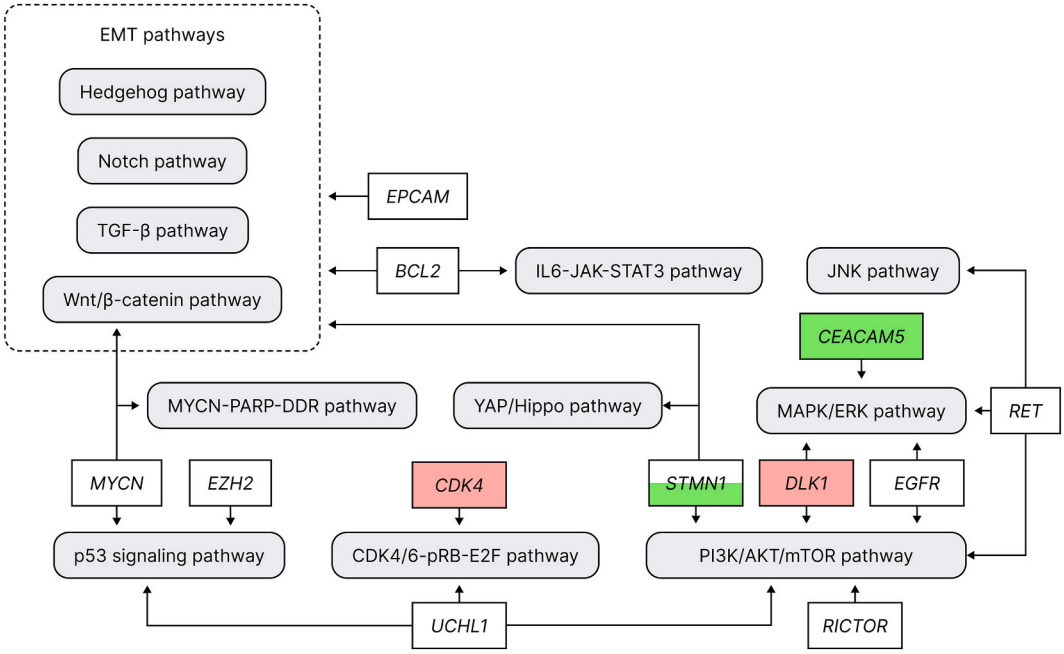

Fig. 4. Complex interplay between cell cycle-related genes and their influence on various signaling pathways in NETs. *EPCAM, BCL2, STMN1,* and *MYCN* influence pathways involved in epithelial-to-mesenchymal transition (EMT) [235–237], with *MYCN* exerting a particular influence on the Wnt/β-catenin pathway [238]. Additionally, *MYCN* influences the MYCN-PARP-DNA damage response (DDR) pathway and the p-53 signaling pathway [239]. *EZH2* and *UCHL1* also interact with the p53 signaling pathway [240,241]. *BCL2* further influences the IL-6/JAK/STAT3 signaling pathway [235]. *CDK4* and *UCHL1* modulate the CDK4/6-pRB-E2F pathway [241], with *CDK4* acting as an inhibitor [242]. *STMN1* enhances the PI3K/AKT/mTOR pathway [243], while *EGFR, RET, RICTOR,* and *UCHL1* exert distinct, yet undefined, effects on this pathway [241,244–247]. *RET* additionally influences the MAPK/ERK and c-Jun-NH2-kinase (JNK) pathways [244]. *DLK1* and *EGFR* impact the PI3K/AKT/mTOR and MAPK/ERK pathways [245,248], with *DLK1* acting as an inhibitor of both [249,250]. *CEACAM5* enhances the MAPK/ERK pathway [251]. The green color represents activation of the pathway, the red color represents inhibition of the pathway, the white color indicates genes with insufficient information for precise evaluation as enhancers or inhibitors, and the gray color indicates signaling pathways.

7. Conclusion

The identification of numerous cell cycle-related genes that promote progression rather than inhibition has provided valuable insights into the molecular mechanisms underlying NB and PCC tumors. Notably, most genes influencing the G1/S phase transition were identified compared to those affecting other cell cycle phases. Among these, *TOP2A* emerged as a crucial marker, with overexpression observed in proliferating tumor cells in both NB and PCC. These findings, with the elevated *MKI67* gene expression, suggest potential common patterns in adrenal gland NETs, including enhanced cell cycle progression in tumor cells that promotes tumor growth.

Given the established role of TOP2A as a therapeutic target in other cancers, exploring its potential in adrenal NETs warrants further investigation. Additionally, the overexpression of *DLK1* in adult and hormone-producing CHCs, as evidenced by recent scRNA-seq studies, aligns with the availability of approved and investigational DLK1-targeted therapies for NETs. Moreover, the ongoing clinical evaluation of drugs targeting cyclins B1/A and EZH2, both implicated in NB tumorigenesis, underscores the importance of exploring these targets in NB.

Both approved and clinical-stage RET inhibitors are currently available for MTC treatment, which aligns with the recent scRNA-seq study demonstrating *RET* overexpression in adult malignant C cells of MTC. These findings strongly motivate further preclinical and clinical investigations into additional potential therapeutic targets. Several proteins encoded by the cell cycle-related genes discussed in this review are targets of drugs currently in preclinical development. Given the promising preclinical data, additional research is essential to evaluate the clinical efficacy and safety of these targets in NETs.

CRediT authorship contribution statement

Ekaterina Filipovich: Writing – original draft, Visualization. **Ekaterina Gorodkova:** Writing – original draft, Visualization. **Anastasia Shcherbakova:** Writing – review & editing. **Walaa Asaad:** Writing – review & editing. **Sergey Popov:** Project administration. **Galina Melnichenko:** Funding acquisition. **Natalya Mokrysheva:** Funding acquisition. **Marina Utkina:** Writing – review & editing, Supervision, Conceptualization.

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