

Review article

The role of E2F2 in signaling pathways associated with cancer pathogenesis and potential treatment: a review of current studies

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ABSTRACT

Introduction and objective. E2F transcription factor 2 (E2F2) protein is the transcription factor that plays an important role in tumorigenesis. E2F2 effects the cell cycle, tumor suppressor proteins, and can also be transformed by proteins of small DNA tumor viruses. The objective of the study is to provide a summary of the current knowledge on the neoplastic pathways that involve E2F2.

State of knowledge. Numerous studies have demonstrated a role for E2F2 in various signaling pathways. Certain components of these pathways may serve as potential targets for oncological therapy. E2F2 has been shown to be associated with neoplasms of various locations and histological types (breast, colon, gastric, laryngeal, liver, lung, ovarian, pancreatic, and prostate cancers).

Conclusions. Further investigations of E2F2 pathways are warranted for a clearer understanding of neoplastic processes and to identify novel pharmacological treatments.

Key words: E2F2, E2F, cancer, transcription factor, oncology, p53, p21

INTRODUCTION

The transcription factors are molecules that affect the rate of transcription of genetic information from DNA to messenger RNA, by binding to a specific DNA sequence [1].

E2F is a family of genes encoding transcription factors critical for regulating the cell cycle. There is increasing evidence that aberrant expression or activation of E2F is common in malignancies. Significant associations have been reported between E2F and carcinogenesis and progression of many types of cancer [2]. E2F factors affect various aspects of tumor development, inducing different effects depending on the cell cycle stage, cell type and the presence of growth factors or inhibitors [3]. E2F family can be divided into three sub-categories: activators – E2F1, E2F2, E2F3; repressors – E2F4, E2F5; and atypical repressors – E2F7, E2F8 [4].

The expression of E2F target genes indicates high E2F activity in almost all types of cancer. It results from various factors such as inactivation of E2F key regulator and main binding partner, Rb (retinoblastoma protein encoded by *RB1* gene, one of the most prominent tumor suppressors disrupted in cancer cells), overexpression of cyclin-dependent kinases (CDKs), or inactivation of CDK inhibitors [5–8]. It is hypothesized that disturbances in the CDK-RB-E2F pathway are a necessary factor for the development of all types of cancer [8–11].

E2F transcription factor 2 (E2F2), like other proteins from the E2F family, plays special roles in regulating the function of tumor suppressor proteins, controlling the cell cycle, and is also a target of transforming proteins of small DNA tumor viruses [12]. E2F2 is also involved in cell proliferation and oncogene-mediated transformation [4, 13–15]. Furthermore, E2F2 plays a role in inflammation [16–18], cell migration [18] and invasion [18, 19] and apoptosis [20]. The role of E2F2 in terms of proliferation, inflammation or apoptosis is bidirectional [21]. E2F2 factor can both inhibit proliferation (as in peripheral blood T lymphocytes) [22] or promote cell division (as in cardiomyocytes) [23]. The role of the E2F2 factor is also complex in the case of apoptosis, where E2F2 inhibits the apoptosis of pancreatic cells [24], but promotes the apoptosis of melanocytes or cone photoreceptor cells [25, 26]. E2F2 may also act as either an “activator” or an “inhibitor” of inflammation. In mouse models, E2F2 acted as a negative regulator of the inflammatory response by inhibiting the proliferation of activated lymphocytes [27]. In nerve tissue, E2F2 may act as an activator of inflammation [28]. E2F2 is referred to as an activator because it activates genes, such as a well-known oncogene – cyclin E [21]. The structure of E2F2 contains several specific domains that enable it to perform its functions. These domains include:

winged-helix DNA binding domain (DBD), a helix-loop-helix binding domain, cyclin A / CDK2 (cyclin-dependent kinase 2) binding domain, Rb binding domain and hydrophobic heptad repeat dimerization domain. The E2F2 dimerization domain enables heterodimerization with DP (Dimerization Partner) family of proteins: DP-1, DP-2 and DP-3. This interaction provides a path to the regulation of cellular functions by creating functional transcription factors capable of binding DNA with high affinity [21, 29, 30].

So far, there have been numerous studies linking E2F2 with tumors of different locations and histological types. This paper summarizes the current state of knowledge regarding the neoplastic pathways in which E2F2 is involved. This information can be the basis for the development of new oncological therapies. The importance of that development may be emphasized by the fact that cancers constitute the second most common cause of death in the world after ischemic heart disease [31].

THE ROLE OF E2F2 IN P53-P21 AXIS REGULATION

As cells progress through different phases of the cell cycle, they undergo several discrete transitions affected by various transcription factors [32]. P53 is a transcription factor and tumor suppressor. In response to various cellular stresses such as DNA damage, p53 accumulates in cell nucleus where it exerts its pro-apoptotic function. By activating its target genes, the activated p53 arrests cell cycle to facilitate DNA repair and/or induces apoptosis to prevent the spread of cells with significant DNA damage [31, 33]. Accumulation of such genomic aberrations could be the cause of the development of cancers [32, 33].

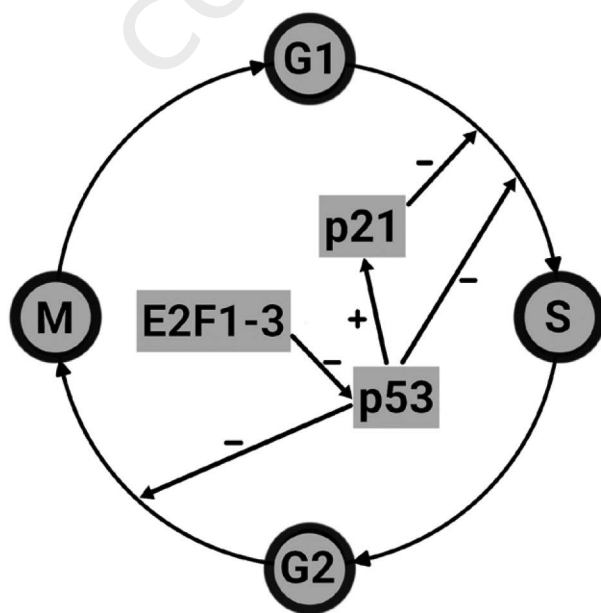
In 2001, Wu et al. [13] demonstrated that the simultaneous inactivation of E2f1, E2f2, and E2f3 resulted in the inhibition of cell proliferation that affected G1/S (G – “gap”, S – “synthesis”) and G2/M (M – mitosis/meiosis) checkpoint transitions in the cell cycle. This blockage coincided with an increase in p53’s transcriptional activity and the upregulation of its target genes, including p21CIP1 (cyclin dependent kinase inhibitor 1A). These findings suggest that the E2f1-3 elimination through mutation, viral oncogenes, or gene targeting strategies mitigates the induction of p53 target genes and the proliferation arrest [13, 15].

These results formed the basis for a study by Sharma et al. (2006) [15]. In mouse embryonic fibroblasts, the deactivation of p21(CIP1) restored the ability of E2f1-3-deficient cells to enter the G1/S transition, but not G2/M transition. Whereas, loss of p53 allowed these cells to progress through both G1/S and mitosis,

resulting in continued proliferation. Notably, the inactivation of p53 (but not p21[CIP1]) made E2f1-3-deficient cells susceptible to transformation and tumorigenesis. These findings suggest that the E2F1-3 factors' negative regulation of the p53-p21(CIP1) axis is vital for cell cycle progression and cellular transformation. According to further investigations in 2007 [14], the p53 activation and the p21(CIP1) upregulation (by the simultaneous inactivation of E2f1, E2f2, and E2f3) results in the inhibition of CDK activity and Rb phosphorylation resulting in a strong repression of E2F target gene expression and a significant blockade of cellular proliferation. In E2f1-, E2f2-, and E2f3-deficient cells, the induction of p21(CIP1) and other p53 target genes was prevented by the inactivation of p53 through spontaneous mutation or conditional gene ablation. Consequently, cyclin-dependent kinase activity, Rb phosphorylation, and E2F target gene expression were almost fully restored to normal levels, making cells responsive to normal growth signals. These findings suggest that the E2F1, E2F2, and E2F3 activators play a crucial role in regulating a p53-dependent axis that indirectly controls E2F-mediated transcriptional repression and cellular proliferation [13–15].

The described interactions have been schematically presented in figure 1. The relationships between E2F2 and other signaling pathways have been described in studies on various types of cancers and are summarized in the subsequent part of the study.

Figure 1. Graphic summary of studies [13–15] illustrating the relationship between E2F1-3 and the p53-p21 axis.



-- inhibitory effect; + – activation; G1, S, G2, M – phases of the cell cycle; E2F1-3, p53, p21 – transcription factors.

PATHWAYS RELATED TO E2F2 DESCRIBED IN VARIOUS TYPES OF CANCER

In the following section of the paper, we summarize previous research that highlights the connections between the E2F2 factor and multiple signaling pathways and factors involved in cell cycle and carcinogenesis. To enhance clarity, the scientific findings are grouped according to the organ from which the tumor originates.

Breast cancer

Breast cancer is the most common cancer in the world and the most common cancer-related cause of death in women [34]. Therefore, it is important to develop knowledge about the etiopathogenesis and potential targets for new drugs that would further reduce the mortality rate for this cancer.

In 2014, Bollig-Fischer et al. [35] investigated the regulatory mechanisms in the human epidermal growth factor receptor 2 (HER2) pathways. HER2 is an oncogene often found in breast cancer. The authors used the SUM-225 line of metastatic breast cancer cells and several analytical techniques, including the novel P metabolic (MP) grammars method. They showed that HER2 increases the expression of E2F2. Importance of that phenomenon in tumorigenesis was additionally confirmed by targeted E2F2 gene knockdown, which inhibited cancer cell-matrix adhesion and outgrowth. That may indicate E2F2 as a potential target in patients with HER2+ breast cancer.

Lin et al. (2020) [36] conducted study on the pathogenesis of breast cancer. Using luciferase assays, they managed to demonstrate the interaction between E2F2 and MiR-638 microRNA. E2F2 was found to be elevated in breast cancer cells and positively correlated with the percentage of CD24-/CD44+ cells and the level of the sex determining Y-box 2 region (SOX2) and octamer binding transcription factor 4 (OCT4). These factors have all been shown to be typically present in breast cancer stem cells. MiR-638 was down regulated in cancer cells and the luciferase assays revealed a negative correlation between the levels of MiR-638 and E2F2. MiR-638, by inhibiting E2F2 was able to halt tumor growth and reduce the ability of breast cancer stem cells to regenerate, proliferate and invade. Therefore MiR-638 may also be a potentially important factor in the treatment of breast cancer.

Colorectal cancer

Colorectal cancer is the second leading cause of cancer-related mortality in the world [30]. The treatment depends on the stage of the cancer and include both surgical methods and systemic treatment in the form of chemotherapy [37].

The study investigating the etiopathogenesis of colorectal cancer and analyzing the role of E2F2 in neoplasms was undertaken by Li et al. in 2015 [38]. The authors conducted a cell viability assay and EdU (ethynyl-labeled deoxyuridine) incorporation assay which showed that miR-31 microRNA promotes colon cancer cell proliferation, while E2F2 inhibits tumor growth. Quantitative real-time polymerase chain reaction (qRT-PCR) revealed that the inhibitory effect of E2F2 was due to the decreased expression of survivin, and the subsequent regulated expression of CCNA2 (cyclin-A2), C-MYC (cellular Myc oncogene), MCM4 (minichromosome maintenance complex component 4) and CDK2. The luciferase assay revealed that the regulatory effect of miR-31 on tumor cell proliferation was due to the targeting of E2F2. The paper may suggest the utility of miR-31 as another potential molecular target in cancer treatment.

The studies presented above reveal that E2F2 is involved in many different cancer-related pathways and it can act as an activator (knockdown or inhibition of E2F2 suppressed cancer outgrowth in breast cancer) or as a tumor suppressor (E2F2 inhibited cancer progression in colorectal cancer).

Gastric cancer

Over one million new cases of gastric cancer are being diagnosed each year over the world, giving the fourth highest incidence and mortality [37].

A study conducted by Wen et al. in 2015 [39] investigated the effect of miR-26a on cisplatin sensitivity in gastric cancer. They also assessed the role of the neuroblastoma RAS virus (*v-ras*) oncogene homolog (NRAS) and E2F2 on the sensitivity to chemotherapy in cases of gastric cancer using the MTS (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium) method and apoptotic cell analysis. The authors showed that miR-26a was downregulated in cisplatin resistant cells and, using gain and loss of function analysis, they revealed that miR-26a can improve the sensitivity of cancer cells to cisplatin. In addition, using luciferase assay, miR-26a was shown to reduce NRAS and E2F2 expression levels. Knockdown of NRAS or E2F2 was found to sensitize gastric cancer cells to cisplatin and therefore by targeting NRAS and E2F2, miR-26a could improve the sensitivity of gastric cancer cells to cisplatin chemotherapy. This study provides evidence of the potential utility of miR-26a as an anti-E2F2 chemotherapy-sensitizer in gastric cancer.

The importance of E2F2 in the pathogenesis of gastric cancer was further investigated by Wang et al. in 2016 [40]. In this study, mi-

croRNA microarray analysis was used to demonstrate that miR-31 microRNA is decreased in gastric cancer. Low miR-31 expression was accompanied by poor tumor cell differentiation, presence of lymph node metastasis, advanced tumor stage, and worse overall survival in gastric cancer patients. In contrast, ectopic miR-31 expression was shown to decrease tumor cell viability, enhance apoptosis, arrest tumor cells in the G1 transition, and reduce tumor cell migration and invasion. Forced miR-31 expression was also shown to inhibit the growth of implanted tumors *in vivo*. Luciferase assays and western blot revealed that E2F2 is a direct target of miR-31. E2F2 expression was increased in gastric cancer tissues and inversely related to miR-31 levels. Downregulation of E2F2 mimicked the anti-tumor activity of miR-31 in gastric cancer cells, however the miR-31 mediated inhibition of gastric cancer cell lines was absent in cells with ectopic E2F2 expression. These results concluded that miR-31 manifests tumor suppressive activity by inhibiting E2F2 expression. Thus, miR-31 may be a therapeutic target for gastric cancer therapeutics.

Yu et al. in 2020 [41] also investigated the association of E2F2 with gastric cancer. In their research, vectors overexpressing or inhibiting H19 (long non-coding RNA H19), miR-138 microRNA and E2F2 genes were constructed and transfected into gastric cancer cells to observe the effects on cell proliferation, invasion, and apoptosis. Results showed that H19 was increased in gastric cancer and was highest in patients with larger (≥ 5 cm) tumor size, high grade (III + IV) cancer, and lymph node metastases. In addition, decreased expression of H19 has been shown to inhibit proliferation and invasion of gastric cancer cells and induce apoptosis. The miR-138 gene was shown to act as a molecular target for H19, and E2F2 could be negatively regulated by the encoded microRNA. Decreased expression of miR-138 or upregulation of E2F2 may therefore attenuate the changes in the biological behavior of gastric cancer cells induced by the H19 decreased expression. The authors concluded that H19 may be used as a biological marker for the diagnosis of gastric cancer and to provide useful prognostic information.

Laryngeal cancer

E2F2 also appears to be implicated in the pathogenesis of laryngeal cancer, a topic that has been investigated by Cui et al. in 2019 [42]. The authors conducted a dual luciferase reporter gene assay, RNA downgrading assay and RNA immunoprecipitation assay to verify the interaction between HOX transcript antisense RNA (HOTAIR), miR-454-3p microRNA and E2F2. Exosome-mediated HOTAIR was found to compete with endogenous RNA (ceRNA) of miR-545-3p microRNA to regulate E2F2 and thus negatively regulate the radiosensitivity of laryngeal cancer cells.

This study provided new insight into the treatment of laryngeal cancer.

Hepatocellular carcinoma

Another example of a study on E2F2 was carried out by Hong and colleagues in 2016 [43]. In this study, the author reported that E2F2 was associated with overexpression of bromodomain-containing protein 4 (BRD4) in three large cohorts of patients with hepatocellular carcinoma (HCC). In addition, JQ1 thienotriazolodiazepine was found to inhibit BRD4, which induced antitumor effects including cell cycle arrest, cell aging, decreased wound healing capacity, and the formation of soft agar colonies in HCC cell lines. SK-Hep1 HCC cells treated with JQ1 were used for gene expression analysis where E2F2 was demonstrated to be the first downstream direct target of BRD4. The key role of E2F2 in the inhibition of BRD4 was later confirmed by the chromatin immunoprecipitation (ChIP) test and the loss of function test. Analysis of the TCGA (the cancer genome atlas) data set and the GSE16757 cohort in NCBI GEO (National Center for Biotechnology Information, Gene Expression Omnibus) data base revealed that the E2F2 overexpression has also been associated with poor prognosis in HCC patients. The regulation of the cell cycle by the BRD4-E2F2 circuit, as it has been shown in this study, may facilitate the development of new therapeutic strategies in patients with hepatocellular carcinoma.

The role of the E2F2 was further investigated by Zeng et al. (2020, 2023) [44, 45], and Shen and Wang (2021) [46]. Both studies concluded that the E2F2 expression is elevated in HCC and that the higher E2F2 expression is related with higher cancer stage and worse overall survival. The overexpression of E2F2 in human liver cancer cell line (HepG2) cells led to a substantial inhibition of apoptosis and the p53 pathway, whereas silencing of E2F2 in HepG2 cells produced the opposite effect [45].

Lung cancer

In 2020, lung cancer was responsible for 1 796 144 deaths worldwide, which makes it the cancer with the highest mortality (almost two times higher than the second highest mortality of colorectal cancer) [44]. Therefore, the researchers are constantly seeking new molecules that could be targets for new treatment methods for lung cancer.

In 2017, Feliciano et al. [47], in a study of 119 lung cancer biopsies, confirmed the association of E2F2 with miR-99a microRNA, the expression of which reduced the proliferation of H1650, H1975 and H1299 lung cancer cells by inhibiting the cell cycle and promoting apoptosis. The authors identified two proteins –

E2F2 and EMR2 (EGF-like, mucin-like, hormone-receptor-like 2) that were downregulated by miR-99a. miR-99a expression was found to prevent cancer cell epithelial-to-mesenchymal transition (EMT) and repress the tumorigenic potential of cancer stem cells. miR-99a was also found to occur more often in adenocarcinomas as opposed to other types of lung cancer. Therefore miR-99a, E2F2 and EMR2 were identified as important targets implicated in the formation of lung tumors and inhibition of these targets by miR-99a leads, *in vivo*, to a reduction in the cancer stem cell population and represses the EMT process.

Zhou and colleagues (2018) [48] used qRT-PCR to demonstrate further association between E2F2 and lung cancer, namely non-small cell lung cancer (NSCLC). In this study it was found that miR-936 microRNA was significantly downregulated in NSCLC tissues compared to normal tissues. E2F2 was shown to be a target gene for miR-936 in NSCLC cells and was associated with its upregulation in these cells. Moreover, the expression of miR-936 was negatively correlated with the expression of E2F2, which was demonstrated, for example, where overexpression of miR-936 induced a decrease in the level of E2F2 expression in NSCLC tissues. The work concluded that miR-936 suppressed NSCLC progression and did so by targeting E2F2.

In a study by Li et al. conducted in 2018 [49], Western blots and immunohistochemical tests were performed on circular RNA (circRNA), with the intention of determining the levels of proteins involved in the E2F2 pathway. Upregulation of circular RNA PVT1 (circPVT1) was detected in NSCLC specimens and knockdown of circPVT1 suppressed NSCLC proliferation, migration and invasion and increased apoptosis of cells. It was found that regulation of the E2F2 signaling pathway resulted in the progression of NSCLC, mediated by circPVT1. Moreover, it was possible to verify using an *in vivo* xenograft model that circPVT1 present in the cytoplasm of NSCLC cells could serve as a competing endogenous RNA to regulate E2F2 expression and may result in tumor formation via miR-125b microRNA dependent pathways.

In 2020, Zhang et al. [50] not only confirmed the role of the PI3K/AKT pathway, but also linked it with E2F2. The PI3K/AKT pathway plays an important role in promoting oncogenesis in lung cancer and in mediating drug resistance. This pathway is implicated in the metastatic capacity of cancers, being associated with highly aggressive malignancies [51]. The authors noted that overexpression of microRNA-519 (miR-519) inhibited the viability of lung cancer cells and that miR-519 upregulation inhibited the phosphorylation of the PI3K/AKT pathway in SPC-A-1 and 95C cells. miR-519 was associated with the inhibition of E2F2

transcriptional activity, thereby reducing the activity of the PI3K/AKT pathway and limiting the development of lung cancer. Furthermore, the E2F2 overexpression reduced the above effect of the miR-519 on the PI3K/AKT pathway.

Other studies have also associated E2F2 with lung cancer. In 2020, Huang et al. [52] described the interaction between miR-3666 microRNA and NNT Antisense RNA 1 (NNT-AS1) or E2F2. They used the starBase v2.0 bioinformatics tool and verified the data with the Dual-Luciferase Reporter test. They used the Western blot method to determine the level of E2F2 protein. The analysis revealed that NNT-AS1 and E2F2 were upregulated, but miR-3666 was downregulated in lung cancer tissues. Knockdown of NNT-AS1 reduced proliferation and invasion and enhanced apoptosis in lung cancer cells. miR-3666 reversed the effects previously induced by NNT-AS1 knockdown and miR-3666 was shown to be a target of NNT-AS1. miR-3666 was also found to directly interact with E2F2 and overexpression of E2F2 led to the reversal of the anti-proliferative and pro-apoptotic effects of increased miR-3666 on lung cancer cells. Thus, it was shown that pro-cancerous effect of NNT-AS1 results from inhibition of miR-3666, which in turn inhibits pro-cancerous E2F2.

Ovarian cancer

Xie et al. [53] investigated the genes that co-regulate E2F2 in ovarian cancer. The authors used raw GDS3592 data from GEO datasets and established that E2F2, as a transcription factor, was significantly upregulated in epithelial carcinoma cells of ovarian cancer. Genes for minichromosome maintenance protein complex 4 (MCM4), cyclin E2 (CCNE2) and nuclear receptor binding SET domain protein 2 (NSD2) were found to be co-regulated with E2F2 in ovarian cancer and forced expression of E2F2 in ovarian cancer cells resulted in an increase in the expression of MCM4, CCNE2 and NSD2. Moreover, it was found that E2F2 was associated with poorer overall survival in patients with ovarian cancer.

In 2019, Zhou et al. [2] analyzed databases, including ONCOMINE, GEPIA, cBioPortal, Metascape and the Kaplan-Meier plotter, in order to investigate the expression and prognostic value of E2F, including E2F2, in patients with ovarian cancer. The value of E2F2 was shown to be overexpressed in ovarian cancer cells of the target population, and therefore may be a possible prognostic biomarker and therapeutic target. Furthermore, the E2F transcription factors mRNA was found to be negatively associated with the tumor stage for ovarian cancer.

More recently, in 2020, Cao et al. [54], analyzed ovarian cancer tissue specimens and found that cancer cells express significant-

ly higher LBX2 antisense RNA 1 (LBX2-AS1) than normal cells. The authors also found an association between LBX2-AS1 and decreased overall patient survival, with knockdown of LBX2-AS1 having a suppressive effect on tumor progression. LBX2-AS1 turned out to indirectly influence the expression of the E2F2 gene; LBX2-AS1 inhibits the action of miR-455-5p and miR-491-5p which, in turn, by affecting mRNA, inhibits the expression of the E2F2 gene in ovarian cancer cells. Forced E2F2 expression was found to reduce the effects of LBX2-AS1 knockdown in ovarian cancer cells.

Pancreatic cancer

The pancreatic cancer's (PC) death rate is still one of the highest – 94% [31]. That is the reason why it is important to constantly seek new methods of therapy.

Expression of long non-coding RNA differentiation antagonizing nonprotein coding RNA (lncRNA DANCR), miR-214-5p microRNA and E2F2 in pancreatic cancer tissues and cell lines was investigated by Yao et al. in 2019 [55] using the qRT-PCR method. Western blot analysis was used to detect E2F2 protein expression in PC cells, and to assess the effect of DANCR on PC cells, a gene knockdown was performed, both *in vitro* and *in vivo*. The regulatory mechanisms of competing endogenous RNAs were obtained from bioinformatics predictions and a luciferase assay. Results showed that there was a significant increase in DANCR in PC cell lines and there was a correlation between high DANCR expression and poor prognosis. In addition, DANCR knockdown was found to inhibit PC cell growth and metastasis. DANCR, via its effect on miR-214-5p, was found to positively modulate E2F2 expression in PC cells. Luciferase assay revealed that E2F2 is overexpressed in PC cells patients. All the above facts may indicate that the DANCR/miR-214-5p/E2F2 lncRNA axis may be a potential target for PC therapy.

Prostate cancer

Prostate cancer is the second most common cancer in men, with the incidence almost equal to lung cancer (1 414 259 vs 1 435 943 new cases in 2020 in men worldwide) [34].

Dong et al. in 2010 [56] investigated if let-7a microRNA precursor, by downregulating E2F2 and cyclin D2 gene (CCND2), acts as a suppressor in prostate cancer. They used a double luciferase reporter assay that showed that 3'UTR E2F2 and CCND2 were directly related to let-7a, and western blot revealed that let-7a decreased E2F2 and CCND2 expression. Prostate cancer xenografts were used to confirm the ability of let-7a to inhibit prostate tumor growth *in vivo*. This study confirmed the relationship be-

tween the antiproliferative capacity of let-7a and the inhibition of E2F2 expression.

These findings could be a starting point for the new therapies for the prostate cancer, particularly for hormone resistant malignancies.

CONCLUSIONS

The above studies demonstrate the significant participation of E2F2 in neoplastic signaling pathways, with the crucial pathways and associated molecules presented in table 1. Increased E2F2 expression in many neoplasms was typically associated with higher tumor aggressiveness, greater tendency to metastasize, and poorer patient prognosis. Furthermore, in some tumors, such as colorectal cancer, E2F2 acted as a tumor suppressor. Modulating the expression of E2F2 and its signaling pathways in individual neoplasms may constitute a new therapeutic direction for cancer patients.

Table 1. The crucial E2F2-related signaling pathway molecules discussed in various types of cancers.

Type of the cancer	Related signaling pathway molecules
Breast cancer	HER2, MiR-638, OCT4, SOX2
Colon cancer	CCNA2, CDK2, C-MYC, MCM4, miR-31, survivin
Gastric cancer	H19, miR-138, miR-26a, miR-31, NRAS
Hepatocellular cancer	BRD4, p53
Laryngeal cancer	HOTAIR, miR-545-3p
Liver cancer	BRD4, JQ1
Lung cancer	circPVT1, EMR2, miR-125b, miR-3666, miR-519, miR-99a, NNT-AS1, PI3K/AKT
Ovarian cancer	CCNE2, LBX2-AS1, MCM4, miR-455-5p, miR-491-5p, NSD2
Pancreatic cancer	DANCR, miR-214-5p
Prostatic cancer	CCND2, let-7a

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