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ARTICLE

Advances in miRNA Research in Hepatocellular Carcinoma

Erqi Li Bin Zheng Jian Li *

Affiliated Hospital of Chengde Medical College, Chengde, Hebei, 067000, China

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ABSTRACT

Globally, Hepatocellular carcinoma (HCC) is recognized as a major malignant tumor, being the 6th most common in terms of occurrence and ranking third in mortality rates among all cancer types. Within China, HCC is noted as the fourth most prevalent cancer and the second most common cause of cancer-related fatalities. The difficulty in managing HCC stems from its tendency to remain undetected due to a lack of symptoms in the early stages, along with the current lack of both effective diagnostic techniques and treatments for chemotherapy.

MiRNA, also referred to as microRNA, is a type of non-coding RNA typically consisting of 19-22 nucleotides in length. Upon binding to the mRNA of target genes, it functions to suppress mRNA translation or induce mRNA degradation, thereby exerting regulatory control over gene expression. Recent research increasingly suggests the pivotal involvement of miRNA in the onset and progression of primary hepatic cells. Studies exploring the association between miRNA and primary hepatic cell carcinoma hold substantial clinical significance in elucidating the pathogenesis, facilitating diagnosis, and advancing treatment modalities for liver cancer.

1. Introduction

Hepatocellular carcinoma (HCC), a prevalent malignant tumor, poses a significant mortality risk. The global incidence of liver cancer continues to escalate[1]. Among primary liver cancers, hepatocellular carcinoma stands as the most prevalent, constituting approximately 90% of cases, while intrahepatic cholangiocarcinoma and mixed hepatocellular carcinoma contribute to a mere 10%[2,3]. In some developing regions of Asia, hepatitis B virus (HBV) emerges as the primary culprit for HCC[4]. Early-stage HCC lacks clinical significance and specific serum markers, resulting in challenges for timely intervention. As HCC advances to later stages, the optimal window for effective treatment diminishes, emphasizing the critical importance of early detection[5]. Hence, there is an urgent need for a reliable serum biomarker to facilitate early diagnosis, treatment initiation, and enhanced prognosis for liver cancer patients.

MicroRNAs (miRNAs), small non-coding single-stranded RNAs within the human body, orchestrate diverse biological activities by modulating downstream target genes[6,7]. In recent years, the progressively unveiled significance of miRNAs has shed light on their role in tumor development, including breast cancer[8], prostate cancer[9], colon cancer[10], and more. A substantial body of literature has emerged, exploring the potential of miRNAs in cancer diagnostics and targeted drug research. This article provides a comprehensive overview of miRNAs and their involvement in the development of hepatocellular carcinoma (HCC). The objective is to deepen our under-

**Corresponding Author:*
Jian Li (1978),
Male, chief physician,
Research direction: Research on the basic pathogenesis of liver cancer;
Email: 2438396213@qq.com

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standing of the mechanisms underlying HCC development and establish the groundwork for utilizing miRNAs as molecular markers for HCC and potential targets for drug intervention.

2. miRNA biology

In 1993, Ambros Laboratories reported the cloning and developmental function of the first microRNA: lin-4, marking a pivotal moment in gene exploration[11]. In 2000, Reinhart et al. demonstrated that another small non-coding RNA, called let-7 (for lethal-7), serves as a crucial regulator in the developmental time series of stem cells in the cryptic nematode Cryptomeria japonica[12-14]. Notably, let-7 was also identified as the first miRNA discovered in humans[14-16]. However, the miRase miRNA database currently catalogues 38,589 mature miRNAs, with over 2,000 sequences representing unique human miRNA genes. In recent years, an increasing number of genes have become implicated in developmental, physiological, and pathological processes[17].

MiRNAs are a class of small, non-coding, single-stranded RNA molecules containing 19-25 nucleotides. miRNAs bind to the 3' end of the target mRNA molecule in response to the interaction of a number of proteins, resulting in either inhibition of translation or specific cleavage of the mRNA molecule induced by the interaction of the target mRNA with the target gene[18,19]. One of the most common modes of cleavage known to date is that miRNAs proceed in an incomplete complementary form with the target gene, thereby blocking it from the target mRNA without causing any interference with its stability, thus preventing its translation from proceeding. miRNAs mainly regulate mRNAs as as initiating or repressing factors involved in tumourigenesis and progression[20-22] . The fact that miRNAs are highly conserved across different species makes this simple class of miRNAs have very critical functions in life activities.

Since their discovery, miRNAs have garnered significant attention in basic medical research, owing to their profound regulatory effects on gene expression and widespread distribution in human tissues and body fluids[18-20]. This characteristic renders miRNAs promising diagnostic markers and therapeutic targets in clinical practice. Notably, miRNAs are actively and passively secreted by tissue cells, and those circulating in the bloodstream exhibit remarkable stability, unaffected by factors such as repeated freezing, pH changes, or RNA degradation. Furthermore, studies indicate minimal gender and inter-individual variations in miRNA expression levels in peripheral blood. These findings underscore the potential of peripheral blood miRNAs as superior diagnostic and therapeutic tools. Presently, the utilization of miRNAs in diverse disease contexts is expanding[23].

3. miRNA expression and mechanism of action in cancer

The miRNA-mediated regulation of gene expression induces cellular stress in response to environmental changes, such as starvation, hypoxia, oxidative stress, and DNA damage[24-26]. This phenomenon is closely associated with human diseases, particularly cancer. MiRNAs involved in cancer regulation can be categorized into oncogenes (oncomiRs) and tumor suppressors. OncomiRs are up-regulated in cancer, suppressing their target oncogenes, while tumor suppressors are down-regulated in malignant tumors, leading to the overexpression of their target oncogenes. Approximately 50% of miRNAs are located at "fragile sites" in the genome, and many of them undergo amplification or deletion in cancer[27-28].

Numerous miRNAs have been identified to be associated with cancer, with a single miRNA exerting effects on multiple cancer types. For instance, the oncogene MiR-155, a validated immune system oncogene[29-30], has been implicated in nasopharyngeal carcinoma and breast cancer in recent studies[31]. In vitro experiments have demonstrated that the overexpression of miR-155 influences the expression of transforming growth factor-beta receptor 2 (TGFβR2), subsequently impacting the proliferation and metastasis of gastric cancer cells[32,33]. Similarly, miR-21 is another miRNA exhibiting elevated expression in various cancers. In ovarian cancer, miR-21 interacts with the 3'-UTR of PTEN mRNA[34]. In lung cancer, miR-21-5p directly targets SMAD7, resulting in a significant up-regulation of SMAD7 in lung cancer tissues[35]. Additionally, the MiR-17~92 family has been demonstrated to be up-regulated in various cancers[36].

MiR-15 and miR-16 function as oncogenes and are located within the intron of the non-protein coding gene LEU2. They act as tumor suppressors in approximately 68% of B-cell chronic lymphocytic leukemia (B-CLL) cases and are associated with lymphoma of the condyloma, multiple myeloma, and prostate cancer[37,38]. The miR-34 family comprises miR-34a and miR-34b/c, which are direct transcriptional targets of p53 and are downregulated in various cancers, including acute myeloid leukemia[39,40]. Conversely, in prostate cancer[41], breast cancer[42], and renal cancer[43], miR-34 has been found to be upregulated, resulting in tumor suppression by inhibiting cell cycle regulation, promoting apoptosis, and reducing cell invasion and proliferation[44].

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4. Mechanisms of miRNA action in hepatocellular carcinoma

In conclusion, miRNAs exert a critical role in the progression of hepatocellular carcinoma and its related diseases. On one hand, they can be targeted to impact viral transcription, as exemplified by miR-199-3p and miR-201, which can inhibit HBV replication[45]. Moreover, HCV possesses two miR-5-binding sites at the RNA 122′UTR of its genome, and binding of the miR-122/Ago2 complex to these sites can stabilize viral RNA and inhibit its degradation[45,46]. On the other hand, miRNAs can also contribute to liver protection or influence the progression of hepatocellular carcinoma by modulating hepatic fibrosis, hepatic lipid metabolism, hepatic inflammation, alcoholic liver disease, and non-alcoholic liver disease.

In liver tissues, oncogenic factors are present. miR-221 is one of the most highly expressed miRNAs in HCC tissues; its overexpression increased the tumorigenicity of hepatic progenitor cells expressing p53-/-myc. In addition, miR-221 overexpression stimulated the growth of tumourigenic murine hepatic progenitor cells targeting DNA damage-inducible transcript 4 (mTOR pathway regulator DDIT4)[47]. miRNA-21 contributes to hepatocarcinogenesis through the promotion of collagen synthesis and fibrogenesis in the extracellular matrix in the liver[48], and the expression level of miRNA-21 was increased in both serum and tissues[49,50], and the expression level was significantly correlated with tumour progression significantly correlated[51]. Correspondingly, oncogenic factors exist in the liver. In HCC, miR-1, which targets MCL101, is downregulated, thereby inducing apoptosis and delaying tumour progression[52], miR-29 plays an important role as an oncogenic factor in various cancers[53], an in vivo HCC study found that the inhibitory effect of miR-29 was due to the suppression of IGF2BP1 proliferation, migration and invasion in HCC cells[54]. Cheng et al.[55] demonstrated that miR-122 is a significant factor in HCC tissues and cells. 122 was significantly inhibited in HCC tissues and cell lines and targeted IGF-1R, ADAM10 and pyruvate kinase M2 (PKM2). And when miR-122 expression was elevated, it reversed the oncogenicity and could hinder the development of HCC in mice. miR-342-3p expression in hepatocellular carcinoma cells showed a significant reduction in cell proliferation, migration and colony formation. Monocarboxylate transporter protein 1 (MCT1) was identified as a bona fide target of miR-342-3p in HCC[56].

5. miRNA as a diagnostic marker for hepatocellular carcinoma

There have been many discoveries of biomarkers that can be used for cancer diagnosis. For example, CEA (carcinoembryonic antigen) can be used as a diagnostic marker for colon cancer, increased PSA (prostate-specific antigen) in prostate cancer has obvious diagnostic significance, as well as AFP and PIVKA-II in hepatocellular carcinoma[57].However, HCC markers are often not able to achieve simple and effective diagnosis, and the significance of persistently increased AFP in the diagnosis of HCC is quite clear, but it is impossible for the general public to monitor AFP for a long time. Long-term monitoring of AFP has been reported to be negative in about one-third of HCC patients. PIVKA-II is often used in the assessment of HCC after surgical treatment [58]. MiRNAs can be released into the body fluids after necrosis, apoptosis and rupture of the cell, or released into the body fluids in tumors, allowing miRNAs to be easily detected and analyzed in both normal and cancerous cells[59]. So miRNAs have greater application prospects in tumor diagnosis[60].In addition miRNAs have certain tissue specificity. In human tissue biopsies of different organs, the expression of miRNAs has certain differences[61]. Hong Z et al[61] investigated the potential utility of circulating miR-122 and let-7 in the diagnosis of early hepatocellular carcinoma, and their sensitivity was comparable to that of AFP based on the serum levels of patients with precancerous nodules of HBV and early hepatocellular carcinoma. Circulating miRNAs are stable in peripheral blood, and miRNAs in tissues will show specificity and therefore are more useful biomarkers for circulating miRNA assessment of HCC.

6. Summary and outlook

MiRNAs serve not only as markers for clinical diagnosis but also as independent prognostic factors and discriminators between early and late tumor stages in certain cancers. Furthermore, they play a crucial role in molecular targeted therapy and tumor immunotherapy[62]. Presently, miRNA mimics are employed to supplement tumor suppressor miRNAs or inhibit tumors using anti-miRs. However, further in-depth studies are required to translate this therapeutic approach into clinical practice.

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ARTICLE

Survey and Analysis of Postoperative Quality of Life in Gynaecological Oncology Patients

Yujing Zhou Fengjuan Yuan* Moyu Shang Xiaoyu Chang Haiyue Huang Shirui Wang Xuanxiang Bian Qixuan Gao Yanan Dai

Pingdingshan University, Pingdingshan, Henan, 467000, China

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ABSTRACT

Goal: To investigate the current status of quality of life of postoperative patients with gynaecological tumours, and to analyse the relevant factors affecting the quality of life of postoperative patients with gynaecological tumours. Method: One hundred and fifty-three postoperative gynecological oncology patients who attended the gynaecology and oncology departments of three tertiary hospitals in Henan Province from June 2023 to March 2024 were investigated by convenience sampling method. The patients' postoperative survival quality was investigated through the General Information Survey Scale and Quality of Life Score Scale. Results: The quality of life measurement scale score of postoperative gynaecological oncology patients in this study was (121.27±10.87), in which there was a difference in the quality of life of postoperative gynaecological oncology patients of different age, education level, marital status, and per capita monthly income of the family, $p<0.05$. Conclude: The quality of life level of postoperative gynaecological oncology patients is generally good, and age, literacy, marital status, and per capita monthly family income are important factors in the postoperative quality of life of gynaecological oncology patients. Healthcare professionals should focus on patients with older age, lower education level, unstable marital status, and poor economic status, and provide personalised targeted interventions to improve their quality of life.

1. Introduction

With the increase of people's life pressure and the change of life rhythm, gynecological tumours have become more and more common. According to the 2020 Global Cancer Statistics Report, there are about 1.35 million new cases of gynecological tumours in the world, which is a common disease endangering women's health at present, and poses a serious threat to women's life and health(Barten and Laan et al., 2021). The incidence of gynaecological tumours has shown a growing trend in China in recent years, with cervical and ovarian cancers accounting for a relatively high percentage of cases, making them a major threat to women's health(Chan and Li et al., 2021).

In recent years, research on gynaecological tumours is being deepened both at home and abroad, from basic research to clinical research, from surgical treatment to adjuvant treatment, new methods and techniques are being explored, such as minimally invasive surgery and

*Corresponding Author:
Fengjuan Yuan,
Email: 450208139@qq.com

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precision radiotherapy, which not only greatly improve the treatment effect, but also significantly reduce the physical trauma of the patients (Sun, 2021).Barten et al.'s research is even more through the magnetic resonance imaging technology (Iuso and Monacis et al., 2022), which offers a precise and accurate target for gynecological tumour patients with precise target radiotherapy regimens, thus improving patient prognosis, enhancing the therapeutic efficacy of gynecological tumours, and prolonging the survival period of gynecological tumours after surgery.

Gynaecological tumours not only destroy the female reproductive system and have an impact on a woman's appearance, but also adversely affect the patient's personal emotions (Aquil and El et al., 2021). With the deepening of health promotion policies, the goal of treating gynaecological tumours has gradually shifted from mere cure or control of the disease to placing more emphasis on the quality of life of gynaecological tumour patients in the postoperative period (Kano and Chen et al., 2021). In the process of surgical treatment, due to the resection of the reproductive system, postoperative radiotherapy and chemotherapy make the patients have their own image disorder, the patients' emotions are in a state of stress for a long time, and it is very easy to produce anxiety, depression, low self-esteem and other bad emotions (Obayashi and Nagamine et al., 2022), the patients will have a sense of discomfort in the organism that is difficult to be described through the subjective and objective language, which will directly affect the process of the recovery of the patients. In the process of postoperative recovery, if there is no good guidance and care, patients will face a series of physical and mental as well as family and social problems, and the quality of life of patients will be significantly affected. At the same time, persistent anxiety and depression will reduce the patient's appetite, leading to low body nutrition and decreased immunity, which will largely affect the quality of life of gynaecological tumour patients after surgery(He and Tong et al., 2021). Post-operative women with gynaecological tumours will suffer from changes in their own image and low self-esteem, which will affect the quality of their sleep and thus their quality of life(Nanthiphatthanachai and Insin, 2020).

Faced with the challenges of mood swings and declining quality of life common to gynaecological oncology patients, scholars at home and abroad have actively sought solutions to improve patients' quality of life through diversified approaches. Among them, psychotherapy plays a pivotal role in postoperative rehabilitation of gynaecological tumours (Mu and Wu et al., 2021). Through the meticulous intervention of professional psychologists, patients are able to gradually establish positive self-knowledge and effectively alleviate negative emotions such as anxiety and depression, thus enhancing psychological resilience and life satisfaction (Li and Gong et al., 2022).

This study investigates the current situation of postoperative life of oncology patients, analyses the factors affecting the quality of life, and gives such patients targeted humanistic care to promote the improvement and enhancement of the quality of life of gynaecological oncology patients after surgery.

2. Objects and Methods

2.1 Subject of the study

One hundred and fifty-three patients with gynecological tumours who attended the gynaecology and oncology departments of three tertiary hospitals in Henan Province from June 2023 to March 2024 were selected by convenience sampling method.

Inclusion criteria: ① Patients who have been diagnosed as gynaecological tumours by pathological biopsy and have undergone surgical treatment. ② Have the ability of independent expression and can accurately and objectively answer the relevant questions raised in this questionnaire.

Exclusion criteria: ① patients who have suffered from major diseases in other parts of the body; ② patients with psychological and mental diseases; ③ patients with unclear expression and unable to describe their feelings accurately.

2.2 Research tools

2.2.1 General information survey

A general information questionnaire was designed on its own after reading the relevant literature and according to the needs of the survey, including age, place of residence, education level, marital status, monthly income level, number of children, a total of six items, which was used to collect the basic information about the participants of the study.

2.2.2 Quality of Life Measurement Scale for Cancer Patients

The Functional Assessment of Cancer Therapy (FACT) scale (Nandakumar and Veeriah et al., 2022)developed by Cella et al. at Rush-Presbyterian-St. Luke's Medical Centre, Chicago, USA, and 12 additional concern entries for specific cancer patients were used. The scale is divided into 5 domains with 39 entries, including 7 physical status, 7 social/family situation, 6 emotional status, 7 functional status, and 12 additional concern entries. A

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5-point Likert scale was used, with a total score range of 0-156, with higher total scores indicating better quality of life. Among them, 0-74 is classified as poor quality of life, 75-104 is classified as fair quality of life, 105-134 is classified as good quality of life, and 135-150 is classified as satisfactory quality of life. The Cronbach's alpha coefficient of the scale used in this paper is 0.877, which meets the conditions for further data analysis.

2.3 Methods of investigation

The questionnaires were distributed to gynecological oncology patients who met the inclusion criteria through the Questionnaire Star applet, the requirements for completing the questionnaires were explained to the patients, and the questionnaires were carried out after obtaining the informed consent, and the questionnaires were also preliminarily examined during the process of questionnaire collection, and no logical errors or irrational settings were detected, which ensured the validity and reliability of the survey data obtained.

2.4 Statistical methods

The data collected in this study were statistically analysed using SPSS26.0 software. Among them, the count data were expressed as frequency and constitutive ratio, and the measure data were expressed as mean ± standard deviation, and the comparison of scores on the quality of life measurement scale of postoperative gynaecological oncology patients with different characteristics was performed by t-test or one-way ANOVA.

3. Results

3.1 General information on the study population

All 153 patients investigated in this study were confirmed by surgical pathology and had been treated with surgical interventions, 33.97% of them were concentrated in the age group of 36-45 years, and 54.56% of them had their place of residence in towns and cities, and the specific information is shown in Table 1.

Table 1. General information of the study population (n=153)

	Classification	Number (persons)	percentage
Age (years)	≤35	38	24.84%
	36~45	52	33.97%
	46~55	45	29.41%
	≥56	18	11.78%
Place of residence	Rural	68	44.44%
	Urban	95	54.56%
Literacy level	Primary school and below	30	19.61%
	Middle/High School	62	40.52%
	Speciality	35	39.87%
	Undergraduate and above	26	16.99%
Per capita monthly family income (yuan)	≤3000	29	18.95%
	3000~5000	54	35.29%
	5000~7000	56	36.60%
	≥7000	14	9.16%
Marital status	Unmarried	10	6.54%
	Married	128	83.66%
	Divorced/Widowed	15	9.8%
Number of children (number)	0	9	5.88%
Project	1	84	54.90%
Age (years)	>1	60	39.22%

3.2 Scores on the dimensions of the Quality of Life Measurement Scale for postoperative gynaecological oncology patients

The scores of the dimensions of the Quality of Life Measurement Scale for postoperative gynaecological oncology patients in this study were physical status dimension (21.31±1.74), social/family status (21.08±2.27), affective status (19.62±2.58), functional status (21.66±1.93), and other (37.58±3.30), with a total score (121.27±10.87) points. Their scores for each dimension of the quality of life measurement scale are detailed in Table 2.

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3.3 Comparison of scores on the Quality of Life Measurement Scale for postoperative gynaecological oncology patients with different characteristics

The results of the survey showed that there were differences in the scores of the quality of life measurement scale among the respondents of different ages, educational levels, marital status, and per capita monthly household income, and the differences were statistically significant. ($P < 0.05$). See Table 3.

Table 2. Scores for each dimension of the Quality of Life Measurement Scale for postoperative gynaecological oncology patients (n=153, points)

Dimension	Entry	Scoring range	entry parity (accountancy)	Score ($\overline{x} \pm s$)
Physical Condition	7	0~28	3.04±0.25	21.31±1.74
Social/Family Status	7	0~28	3.01±0.32	21.08±2.27
Emotional	6	0~24	3.27±0.43	19.62±2.58
Functional Status	7	0~28	3.09±0.28	21.66±1.93
Other	12	0~48	3.23±0.275	37.58±3.30
Total	39	0~156	3.11±0.28	121.27±10.87

Table 3. Results of univariate analysis of postoperative quality of life in gynaecological oncology patients ($\overline{x} \pm s$ 分)

Project	Grouping	number of examples	Quality of life score	t/F	P
Age (years)	≤35	38	127.47±5.12	70.25	<0.01
	36~45	52	128.29±6.99		
	46~55	45	114.02±7.56		
	≥56	18	106.00±8.90		
Place of residence	Rural	68)	119.35±9.74	0.83*	0.41
	Urban	95	120.53±8.41		
Educational level	Primary school and below	30	115.47±11.02	13.54	<0.01
	Middle/High School	62	118.11±10.53		
	Speciality	35	127.51±8.07		
	Undergraduate and above	26	127.08±8.24		
Marital status	Unmarried	10	119.14±13.07	20.701	<0.01
	Married	128	123.18±9.45		
	Divorced/Widowed	15	106.20±9.54		
Per capita monthly family income (yuan)	≤3000	29	110.41±10.77	28.142	<0.01
	3000~5000	54	118.91±7.99		
	5000~7000	56	127.88±8.69		
	≥7000	14	126.43±7.57		
No. of children ((个))	0	9	119.67±9.30	0.102	0.9
Project	1	84	121.36±11.05		
Age (years)	>1	60	121.38±11.07		

Note: * is a t value

4. Discussion

4.1 Analysis of postoperative quality of life scores of gynaecological oncology patients

As can be seen from the findings in Table 2, the total score of the Quality of Life Measurement Scale for Postoperative Patients with Gynaecological Tumours was (121.27±10.87), which is a good score for quality of life, indicating that the patients with gynaecological tumours in this study were more satisfied with the quality of their life after the operation, and this result is in agreement with the findings of the study conducted by Feng Qian (Obayashi and Nagamine et al., 2022). In the results of this survey, regarding the scores of the dimensions of the Quality of Life Measurement Scale for postoperative gynaecological oncology patients, the scores, in descending order, were

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emotional status, other, functional status, physical status and social/family status.

Patients with gynaecological oncology had the highest scores in the emotional status dimension. The reason for this may be analysed as follows: although the disease brings a great deal of psychological pressure, physical changes, and produces a change in social roles(He and Tong et al., 2021), different patients may show different emotional responses when facing the tumour, which can have a significantly different impact on changes in the quality of life in the postoperative period. Some patients with gynaecological oncology have good coping mechanisms and psychological resilience, and then they are often able to support themselves in maintaining a positive emotional state by tuning into themselves when faced with stresses due to illness and surgery (Nanthiphatthanachai and Insin, 2020). Good emotional state can not only promote the recovery of postoperative health to a great extent, but also relieve patients' physical and mental discomfort to a certain extent, thus improving their postoperative quality of life (Huang and Lin et al., 2021).

In this research survey, the social/family status dimension scored the lowest, and the reason for the analysis is that when suffering from the double trauma of disease and surgery, gynaecological oncology patients need more support from the family and the society, and some studies have shown that there is a positive correlation between the psychological health of patients with gynaecological oncology and the level of social support after surgery(Mu and Wu et al., 2021), and if the If patients can receive timely psychological support from their families after surgical treatment, their quality of life will be improved, on the contrary, patients who do not receive positive emotional feedback from their families will experience a significant decrease in their quality of life (Li and Gong et al., 2022). The physical condition score of postoperative gynaecological oncology patients was (3.04±0.25), which was slightly higher than the social/family condition score, and the reason for this may be that although the surgical trauma and postoperative complications associated with reproductive system diseases have a greater impact on the patients' physical condition, and the patients generally believe that their physical condition after the operation is not as good as before, and there is a situation in which their heart is more than willing to do the job, in order to avoid increasing the burden on their families, the patients will still go through postoperative rehabilitation. However, in order to avoid adding burden to the family, patients will still consciously improve their health quality through postoperative rehabilitation exercises (Choi and Cho, 2022).

Healthcare professionals should pay attention to the health guidance of patients' caregivers, help patients establish strong family support, instruct caregivers to give more care and love to patients, help patients re-establish their enthusiasm for life, and face the disease with a positive and sunny mindset, and pay attention to the postoperative needs and changes of gynaecological oncology patients' physical, social/family, and emotional conditions, so as to timely take positive measures to intervene (Jin and Guo et al., 2022).

4.2 Factors affecting postoperative quality of life in gynaecological oncology patients

4.2.1 Influence of age factors on postoperative quality of life in gynaecological oncology patients

As can be seen in Table 3, the postoperative quality of life scores of gynaecological oncology patients show a decreasing trend with increasing age, and Choi's (Choi and Cho, 2022) study also showed that the older the patient, the worse the quality of life of the oncology patients. In this study, about 40% of the women were older than 46 years old, and women in this age group may be experiencing menopause or perimenopause, and are prone to mood swings and irritability, which, coupled with the effects of the tumour, may further reduce the quality of life of women. Secondly, the older the patients are, the more their physical state will age, and the increased incidence of some underlying diseases that may occur in their own organisms, such as hyperglycaemia, hypertension, hyperlipidaemia, etc., will aggravate the patients' physical burden and affect their quality of life (Jin and Guo et al., 2022).Chitkumarn et al. showed that the younger the age of the post-surgical cervical cancer patients, the stronger the self-management ability and the higher the quality of life(Chitkumarn and Rahong et al., 2022). Therefore, the age factor will have an impact on the quality of life of postoperative gynaecological oncology patients to a certain extent. In order to improve the quality of life of postoperative gynaecological oncology patients, healthcare professionals need to pay attention to the specific needs of different age groups and provide personalised medical and social support services.

4.2.2 Impact of different literacy levels on postoperative quality of life of gynaecological oncology patients

As can be seen from Table 3, the higher the literacy level, the higher the quality of life scores of the patients, the results of this survey the lowest scores of patients with primary school and below, this result is consistent with the results of Falzarano's study (Nandakumar and Veeriah

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et al., 2022). The reason for this may be that patients with different literacy levels have different levels of knowledge about the disease. The higher the literacy level of the patients, the more objective they can be about the disease through self-learning, and the more they can use certain means of guidance to reasonably regulate their own state of mind, face the disease with a positive and optimistic attitude, and better face the changes brought by the disease to their own bodies. On the other hand, patients with a lower level of education are mostly in a passive learning state, and their knowledge of the disease and health education often comes from healthcare personnel, and the information resources they obtain are limited, so they will have more negative emotions towards the discomfort brought by the disease and the change in the quality of life, and it is difficult to improve them through their own regulation, which will then affect the quality of life (Yamamoto and Yoshida et al., 2020). Therefore, healthcare professionals should focus on postoperative gynaecological oncology patients with a low level of literacy, strengthen communication and help them establish confidence in facing the disease positively and improve their quality of life.

4.2.3 Impact of marital status on postoperative quality of life of gynaecological oncology patients

From the results of the study in Table 2, it can be seen that patients whose marital status is married have higher quality of life scores and those who are divorced or widowed have the lowest quality of life scores, indicating that there is an impact of marital status on the postoperative quality of life situation of gynaecological oncology patients. The reason for this may be that family stability not only provides more emotional support to the patient, but also provides strong financial support(Ortiz, 2023). Married patients tend to have already had a reproductive history and accomplished their reproductive goals, so the importance placed on the reproductive system and the need for sexuality will be somewhat lower than that of unmarried patients. Unmarried patients, on the other hand, have higher expectations of reproductive system functioning and sexual quality of life, and therefore rate their quality of life lower. In addition, some studies have shown that marital status is an independent influence on the quality of life of postoperative patients. Therefore, healthcare providers should adopt appropriate health education during the treatment process to improve the knowledge of unmarried and divorced postoperative gynaecological oncology patients, to help them better cope with their own changes and to obtain more psychological support(Ortiz, 2024).

4.2.4 Impact of per capita monthly household income on postoperative quality of life of gynaecological oncology patients

As shown in Table 3, with the change in per capita monthly family income, the postoperative quality of life scores of gynaecological oncology patients also produce a change. Among them, patients with per capita monthly family income ≥7000 had the highest quality of life score of (126.43±7.57); patients with per capita monthly family income ≤3000 had the lowest postoperative quality of life score of (110.41±10.77), so it can be concluded that the quality of life of patients with gynaecological tumours in the postoperative period decreases as the lower the family income is, which is consistent with the results of the study by Parse(Parse, 2021). The reason for this analysis may be that due to the complex and expensive treatment of tumours, the duration of treatment and the long recovery period after treatment, postoperative patients are more likely to face weakness, lack of energy and many discomforts caused by the side effects of medication, and they may feel anxious and depressed due to problems such as financial difficulties of their families(Haidopoulos and Pergialiotis et al., 2024). On the contrary, patients with higher per capita monthly household income tend to have more financial resources to cope with the various challenges posed by the disease(Zhu and Wang et al., 2020). They can choose better healthcare coverage options and receive more advanced and comprehensive treatments, thereby reducing the negative impacts of illness on physical health and quality of life. Therefore, family economic status as reflected by per capita monthly family income becomes an important influence on the postoperative quality of life scores of gynaecological oncology patients. We call on the healthcare-related departments to continue to improve and implement policies to improve the healthcare environment, so as to reduce the problem of oncology patients not being able to receive good treatment results due to their financial situation during the process of seeking medical treatment.

5. Conclusion

The overall postoperative quality of life of gynaecological oncology patients is in good condition and needs to be further improved. There are differences in the postoperative quality of life of gynaecological oncology patients with different age, education level, marital status, and per capita monthly family income. Improving the quality of life of gynaecological oncology patients after surgery requires the joint efforts of healthcare professionals, patients and their families as well as all

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sectors of the society, and only through a comprehensive approach and multiple measures can the quality of life of gynaecological oncology patients be effectively improved and the prognosis be enhanced.

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ARTICLE

Brain Cancer Treatment with Gene Editing

Zihan Qiu Chunjing Liu*

1. International Department of Shaanxi Normal University Affiliated Middle School, Xi'an, Shaanxi, 710061, China
2. Shaanxi Normal University Affiliated Middle School, Xi'an, Shaanxi, 710061, China

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ABSTRACT

The first method is used gene editing to knock out the PD-L1 receptor located on the T cell surface so that PD-1 on the cancer cell surface cannot combine with the PD-L1, in that case, T cell can identify the abnormal cell and kill it. At the beginning, researchers use protein-guided editing technology, but it is not easy to control and not specific enough, so they choose to use CRISPR-Cas9 to edit the target gene. Comparing with the traditional protein-guided nucleases, CRISPR-Cas9 system is more easy-handle, highly specific, and it is an more efficient tool for engineering eukaryotic genomes; because CRISPR-Cas9 system aims to edit the targeting genes by tiny RNAs guiding the Cas9 nuclease to the target site by base pairing.The second treatment is mainly used "fighting cancer with cancer".Because living tumor cells have the ability to home and target tumors, thus, if those living tumor cells can be engineered to secrete therapeutic agents, the tumor cells can be effectively cured. Shah's team picked the agent interferon-β (IFN-β). However, this idea of treatment is limited by the premature cell death due to autocrine toxicity.The researchers solved this problem by first using CRISPR Cas9 to knock out the IFN-β–specific receptor (IFNAR1) in inherently IFN-β–sensitive syngeneic tumor cells, and subsequently engineered them to constitutively produce IFN-β for tumor cell targeting and simultaneous immunomodulation. These therapeutic cells are further designed to coexpress granulocyte-macrophage colony-stimulating factor (GM-CSF) that facilitates the differentiation, proliferation, and recruitment of dendritic cells (DCs). The last approach can stop cancer cell repairing their DNA when it gets damaged.

1. Introduction

Brain tumors are short for intracranial tumors, which often cause neurological dysfunction and can be life-threatening in severe cases. Brain tumors are classified into benign and malignant tumors just like other parts of the body. Meningiomas and pituitary tumors are benign tumors of the brain with high incidence rates. Meningiomas and pituitary tumors are benign brain tumors with a high incidence rate. The term "brain cancer" usually refers to malignant brain tumors, and glioma is the most common type of brain cancer. Gliomas are the most common type of brain cancer. Most brain malignant tumors recur and have a high rate of disability

**Corresponding Author:*
Chunjing Liu,
Female, graduated from China Pharmaceutical University;
biology teacher at the International Department of Shaanxi Normal University Affiliated Middle School, with four years of teaching experience;
Research direction: multiple specialized fields of biology, such as cell biology, microbiology;
Email: 937395589@qq.com

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and mortality, and are one of the key challenges for neurosurgery to overcome. Like most cancers, the cause of gliomas is still unclear, and the prevailing view is that genetic variations in individual cells in the body are the source factors leading to the development of gliomas. Factors such as the environment, food, emotions, and infections may all lead to cell mutations(Wang et al., 2023).

Genome Editing, also known as genome engineering, is a type of genetic engineering that involves the insertion, deletion, modification or replacement of DNA in the genome of a living organism. The difference between this and earlier genetic engineering techniques is that earlier genetic engineering techniques randomly inserted genetic material into the host's genes and genome, whereas gene editing inserts gene fragments at specific locations. Several approaches to genome editing have been developed. A well-known one is called CRISPR-Cas9, which is short for clustered regularly interspaced short palindromic repeats and CRISPR-associated protein 9. CRISPR-Cas9 technology, in essence, is more like a pair of scissors that cuts the DNA and then uses the cell's own repair to control the failure of a particular gene. This technology, after continuous testing to ensure the accuracy of gene editing, can be used to treat diseases caused by genetic mutations, as the trait cannot be expressed when the disease-causing gene is disabled, thus achieving therapeutic effects.

2. Treatment 1

In the immunotherapy field, T cells have one negative regulator is PD-L1, which can combine with dentritic cells(DCs) or tumor cells and recognize the PD-1 receptors on these cells, then, PD-L1 will act on the PD-1 to kill the DCs or tumor cells. They have proved a new method breaking the checkpoint of T cells is useful and feasible(Su et al., 2019). This result gives a new way for targeting checkpoint inhibitors, improving the curative effect of T cell based adoptive therapies as well. On the other hand, scientists have already discovered that the immunization caused by tumor vaccines and cancer vaccines does not always bring the clinical advantage. It must be noted is that a large percentage of tissues are relayed on PD-L1 expression, since PD-L1 influences the limitation of T cell reaction, thus, using medicines to break the tolerance of PD-L1 and PD-1 blocking antibodies still has risks. In that case, recently, RNA-guided endonucleases has been invented, called CRISPR(clustered regularly interspaced short palindromic repeats) and CRISPR-associated (Cas) 9. Comparing with the traditional protein-guided nucleases, CRISPR-Cas9 system is more easy-handle, highly specific, and it is an more efficient tool for engineering eukaryotic genomes; because CRISPR-Cas9 system aims to edit the targeting genes by tiny RNAs guiding the Cas9 nuclease to the target site by base pairing. In their previous work, they have used mice and rats to achieve the efficient gene targeting by so-injection of single cell embryos with Cas9 mRNA and sgRNA. After that, they succeeded finishing similar experiments in Cynomolgus monkeys.

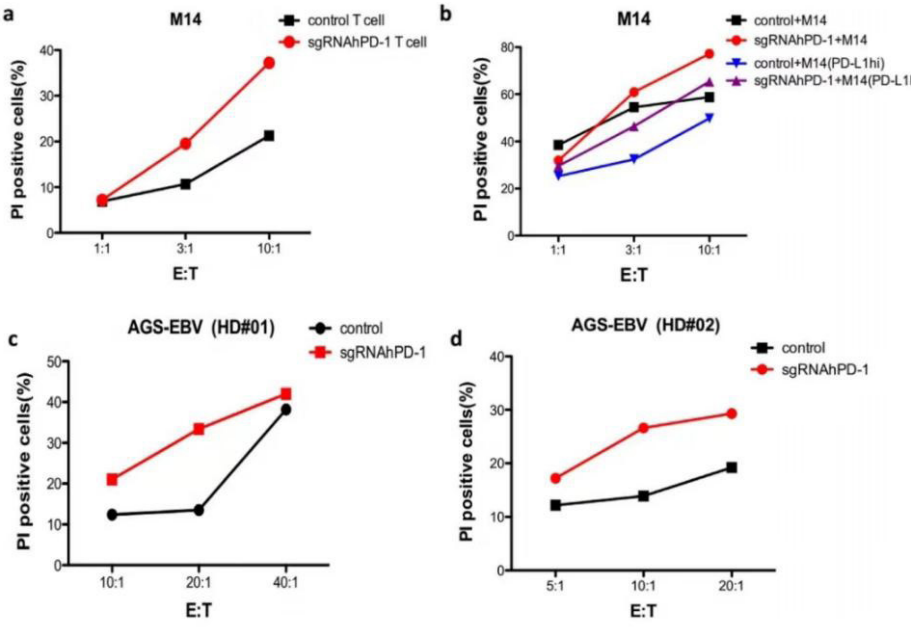

Figure 1. Enhanced cytotoxicity of the hPD-1 KO primary T-cells(Su et al., 2019)

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Patient or healthy volunteers contributes to the T-cell reprogrammed by sgRNA:Cas9 or control were cultured in vitro with IL-2 to co-culture with PD-L1 expressing tumor in different effectors to target cell ratio(E:T). The cytotoxic reactivity of the effector T-cells was measured using CFSE/PI cytotoxicity assay. Fig.1 illustrates the relative percentage of double-positive cells out of CFSE-labeled tumor cells. In graph (a), the hPD-1 KO T cells oor control T cells from melanoma patient were co-cultured with CFSE labeled M14 cells at E:T of 1:1,3:1, 10:1 respectively. After 6 hours, PI was added and the cells were analyzed by flow cytometry. In graph(b), the hPD-1 KO T cell or control T cells from a melanoma patient were co-cultured with CFSE labeled PD-L1-lo-M14 or PD-L1-hi-M14 cells at E:T of 1:1, 3:1, 10:1, respectively. After 6 hours, PI was added and the cells were analyzed by flow cytometry. In graph (c) and (d), the hPD-1 KO T cells or control T cells from healthy donor #01 and healthy donor #02 were co-cultured with CFSE labeled AGS-EBV cells at ratio (E:T) of 5:1, 10:1, 20:1, or 10:1, 20:1, 40:1, respectively. After 16 hours, PI was added and the cells were analyzed by flow cytometry. The above experiments have been repeated 3 times with similar results(Su et al., 2019).

The key problem of immunotherapy is the effective activation of tumor reactive T cells and the inhibition of checkpoint inhibitor. The latest result of the checkpoint blockade targeting the PD-1 or PD-L1 pathway has shown significant antitumor responses in patients with advanced melanoma, lung cancer, and other cancers with a durable clinical response. T cells activated in the absence of PD-L1 or PD-1 co-stimulation are functionally activated, exhibiting increased proliferation by stimulating dc or tumors, producing higher levels of Th-1 cytokines, particularly IFN-γ, IL-2, and TNF-α, and enhancing lytic activity. Previous studies have demonstrated that blocking PD-1 or PDL1 with monoclonal antibodies can improve IFN-γ production and cytotoxicity *in vitro* and *in vivo*. Here, they also demonstrated that these sgRNA hPD-1:Cas9-modified primary T cells from healthy donors or advanced cancer patients exhibit enhanced IFN-γ production by stimulation of relevant peptide antigens, and they found that disruption of PD-1 improved tumor cell lysis, possibly due to PD-1 or PDL1 interaction-mediated reversal of immune resistance. IFN-γ is one of the Th1 cytokines, which mediates cellular immune responses, activates cytotoxic T cells, and indirectly regulates tumor lysis through multiple mechanisms. Therefore, they believe that IFN-γ indirectly activates cytotoxicity in their case. Furthermore, in their system, gene editing using Cas9:sgRNA-mediated T cells from patients and healthy donors elucidated cytotoxic improvements in tumor cell lines on two PD-L1-positive target cell lines, and further confirmed this by inducing PD-L1 expression on target cells. In order to obtain good results using PD-1 or PD-L1 inhibition strategies, the expression of its receptor PD-L1 should be considered. They have used a lot of approaches, such as ethics statement, plasmid expression vectors, T cell activation and electroporation, *in vitro* generation of autologous DC, *in vitro* expansion of PD-1 KOT cells, and flow cytometry. If this method is used in the brain cancer treatment, the PD-L1 on the surface of the T cell are broken *in vitro*, and then inject the modified T cell into the brain, then the modified T cell will attack the cancer cells in the brain, since there are no PD-L1 combined with PD-1, so the cancer cells cannot hide or escape from the assault from T cell.

3. Treatment 2

Researchers found a way to eliminate brain tumor cells efficiently via CRISPR Cas9. The main idea is to repurpose cancer cells to develop a therapeutic that kills tumor cells and stimulates the immune system to both destroy primary tumors and prevent cancer. They transformed living tumor cells into potent agent that drives both tumor killing ability and antitumor immunity.

Once researchers tried using inactivated therapeutic tumor cells (ThTCs) in order to trigger robust immune cell trafficking to the tumor site, resulting in the induction of an antitumor immune response in different cancer types. Yet this approach showed no clinical benefit, due to the lack of direct cytotoxic effect on tumor cells and the inability to trigger a strong antitumor immune response.

In contrast, living tumor cells have the ability to home and target tumors. Thus, if those living tumor cells can be engineered to secrete therapeutic agents, the tumor cells can be effectively cured. They picked the agent interferon-β (IFN-β), owing to its direct effects, such as inhibition of tumor cell proliferation and angiogenesis, and indirect effects, such as activation of antitumor immune responses. However, this idea of treatment is limited by the premature cell death due to autocrine toxicity.

The researchers solved this problem by first using CRISPR Cas9 to knock out the IFN-β–specific receptor (IFNAR1) in inherently IFN-β–sensitive syngeneic tumor cells to avoid autocrine toxicity, and subsequently engineered them to constitutively produce IFN-β for tumor cell targeting and simultaneous immunomodulation. These therapeutic cells are further designed to coexpress granulocyte-macrophage colony-stimulating factor (GM-CSF) that facilitates the differentiation, proliferation, and

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recruitment of dendritic cells (DCs). GM-CSF expression promotes DCs' capacity for antigen cross-presentation, costimulatory molecule expression, and proinflammatory cytokine production, thereby priming the immune system for long-term antitumor responses.

To eliminate the possibility of unwanted secondary tumor initiation, we implemented a dual safety kill-switch comprising herpes simplex virus–1 thymidine kinase (HSV-TK) and rapamycin-activated caspase 9 (RapaCasp9) in these ThTCs(Chen et al., 2023). The switch can be activated if needed to eradicate the ThTCs, making this dual-action cell therapy safe, applicable, and efficacious. These ThTCs were tested in mice with advanced glioblastoma; different mice strains were used, including one that contained bone marrow, liver, and thymus cells derived from humans, mimicking the human immune microenvironment. It was found that the therapeutic tumor cells could eliminate the tumors efficiently, significantly increasing survival rates and providing long-term immunity against recurrent and metastatic cancer(Chen et al., 2023).

Through contrast groups in experiment, researchers found that stimulating type I IFN signaling activities within the tumor microenvironment is likely to improve therapeutic efficacy for patients with cancer.

Also, it has been confirmed that IFN-β is the ideal therapeutic agent since IFNAR1/2 are expressed at the mRNA level with a relatively low range of variations across different types of cancer samples. Similarly, IFNAR1/2 was expressed universally across different IFNreg clusters. Being one of the most aggressive and immunosuppressive tumor types, primary and recurrent glioblastoma (GBM) in TCGA were specifically verified to have a comparable expression of IFNAR1/2. Hence, it is proved that making IFN- β the agent is widely applicable for tumor targeting(Chen et al., 2023).

4. Treatment 3

In an effort to get more people out of their predicament, there are now a variety of methods for treatment. This treatment stop cancer cells repairing their DNA when it gets damaged. They do that by blocking the PARP (poly adenosine diphosphate- ribose polymerase) protein. The class of PARP inhibitors is the most established of the DNA damage response modifiers. They are understood to prevent the DNA damage repair through several mechanisms. PARP also have essential roles in homologous recombination, non-homologous end joining and alternative end joining. In order to maintain normal physiological functions, cells must have multiple DNA damage detection and repair mechanisms to enable timely and accurate repair of damaged DNA.When single-strand DNA is damage, it can repair by mismatch repair, nucleotide excision repair or base excision repair. Whereas the double-strand DNA can only be repaired by homologous recombination (HR) or non-homologous end joining (NHEJ) . PARP inhibitors sometimes interferes with the base excision repair pathway.

The class of PARP inhibitor is the most established of the DNA damage response modifiers and canonically interferes with the base excision repair pathway. Through figure 2, there are about three stages of PARP inhibitors action involved in the process called RARylation.

When the single-strand DNA breaks, it drives double-strand DNA breaks. In the case of double-strand breaks, it is rare, but the situation is much more serious, and if it is not repaired in time, the cell's DNA becomes unstable and the cell eventually dies. So there are two main ways to repair double-stranded DNA breaks. One is non-homologous end-joining (NHEJ) repair, which is more like an emergency fire-fighting captain, whether the repair is correct or not, to connect the broken DNA. The other is the homologous recombination (HR) repair pathway, which involves a large number of proteins such as BRCA, ATM, RAD51, etc.. , of which the most well-known is the BRCA protein. BRCA1 and BRCA2, they are both genes that produce tumor suppressor proteins, which help the body repair damaged DNA, thus ensuring the stability of the cellular genetic material. When these genes are mutated, tumor suppressor proteins are not formed properly, which leads to DNA damage repair method, homologous recombination, being affected as well. BRCAI/2 is a component of the HR pathway. For BRCA-associated malignancies, patients carry a germline BRCAI/2 mutation at one allele in all cells, followed by the complete loss of the second allele in cancer cells, which is a mandatory step in carcinogenesis. HRD is due to the deletion of the BRCAI/2 allele in the cancer cells, and therefore when used in conjunction with a PARP inhibitor, the synthetic lethality would be tumor-specific and will not affect normal cells(Sim et al., 2022).

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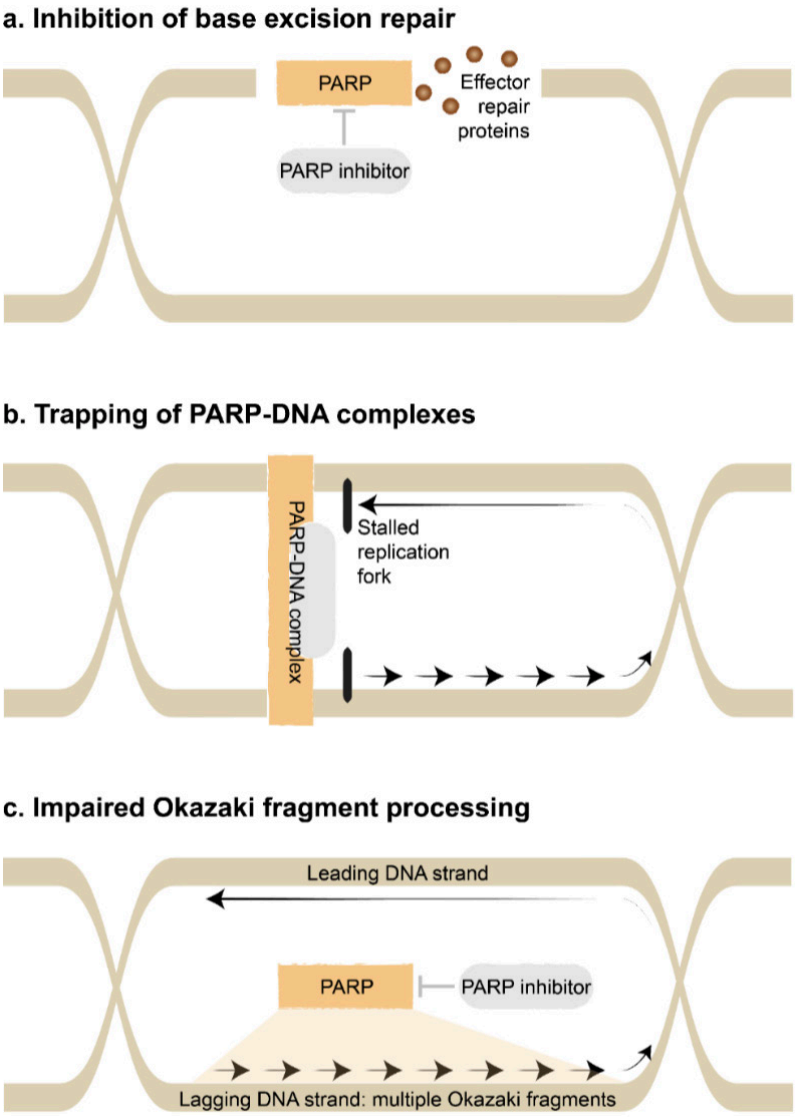

Figure 2. In (a) As soon as PARP discovers a gap in the cytotoxic DNA where a single strand break exists, it binds to it, and this binding activates the catalytic activity of PARP inhibitors. Later in (b), as the PARP inhibitors-PARP-DNA complex accumulate, it cause the replication fork to stall and collapse. (c), PARP acts as a chaperone for the multiple Okazaki fragments in the lagging strand DNA strand during replication, and this is also blocked by PARP inhibitors. Current research suggests that DNA damage repair-dependent PARPs mainly include PARP-1 and PARP-2, both of which accurately recognize DNA wounds and bind intimately to DNA. In the process of repairing DNA damage, PARP-1 plays more than 90% of the function. It works by binding to DNA damage sites (mostly single-stranded DNA breaks) and catalyzes the synthesis of poly ADP ribose chains on protein substrates and recruits other DNA repair proteins to the damage site to repair the DNA damage. PARP inhibitors result in the inability of PARP proteins to shed from DNA damage sites by binding to the PARP1 or PARP2 catalytic site(Sim et al., 2022).

5. Conclusion

In conclusion, the first is to use CRISPR Cas9 technology to edit T cells, removing the PD-L1 receptor on the surface of T cells *in vitro*, so that PD-L1 cannot bind to PD-1 on the surface of cancer cells, thereby attacking cancer cells. The second method is to use CRISPR Cas9 technology to edit the IFN-β receptor of cancer cells, allowing the edited cancer cells to attack other cancer cells and tumor cells to achieve the purpose of treatment. The third approach is to use radiation therapy to destroy the DNA of cancer cells, and then implant PARP inhibitors, so that DNA repair is blocked, so that DNA inactivation can be used to remove cancer cells. From our perspective, the first method is successfully used mice and rats, even in Cynomolgus monkeys to achieve

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the efficient gene targeting by so-injection of single cell embryos with Cas9 mRNA and sgRNA. In addition, it is an more comprehensive, because it is not easy to ignore any cancer cells, but this system attack other normal cells by accident. The second one is lack of clinical experiment, although it is relatively perfect in theory, since it will not attack normal cells or omit cancer cells. And the last one, is limited to the time period, which is only suitable in the gene repairing, but it is the only one, in these three methods, widely used in the clinical treatment, especially in the ovarian cancer treatment.Although PARP inhibitors have limitations in the treatment of brain cancer, PARP inhibitors have benefited patients with breast, pancreatic, and ovarian cancers that carry BRCA gene mutations and are widely used in medicine.However, by targeting the DNA damage repair pathways, PARP inhibitors cause an accumulation of DNA damage and genomic instability. Additionally, the first two approaches are used in CRISPR Cas9, this gene editing technology, comparing with the traditional protein-guided nucleases, CRISPR-Cas9 system is more easy-handle, highly specific, and it is an more efficient tool for engineering eukaryotic genomes; because CRISPR-Cas9 system aims to edit the targeting genes by tiny RNAs guiding the Cas9 nuclease to the target site by base pairing.

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