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Recent treatments for Hepatocellular Carcinoma Cancer(HCC): Update and outlook

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Abstract. In the US, hepatocellular carcinoma (HCC), which accounts for 75%–85% of instances of liver cancer, is a substantial cause of cancer-related fatalities. This review focuses on the recent developments in managing HCC, specifically through Trans-arterial Chemoembolization (TACE), which is currently first-line recommended and boasts a high survival rate. We have also discussed gene therapy, which aims to correct or replace faulty genes contributing to HCC development. Although it is still on trial, early results show promise. There are also various treatments such as OLT, molecularly targeted therapy, radiation therapy, locoregional therapies, gene therapy and immunotherapy. We have also come up with an innovative idea of creating a therapeutic vaccine using circRNA instead of mRNA, along with LNP, to treat HCC. This approach combines the benefits and functions of both circRNA and LNP. Different components of LNP aid in diverse benefits, to name but a few, stability, encapsulation and delivery efficiency, and higher targeting specificity. The use of circRNA offers adjuvant to immune response and better stability. Recent studies suggest that this hypothesis is theoretically possible. A better understanding of the hazardous disease could lead to the development of more effective treatments, which are urgently needed.

Keywords: Hepatocellular Carcinoma (HCC), TACE, chemotherapy, immunotherapy, LNP-circRNA therapeutic vaccine

1. Introduction

1.1. Mortality and current situation of HCC: An overview

In the US, hepatocellular carcinoma (HCC) ranks ninth in terms of cancer-related death. Other names for it include hepatic tumors, hepatomas, and primary liver cancers. To elaborate, 20,000–25,000 persons in the US are diagnosed with HCC each year, which accounts for 75%–85% of all liver cancer cases and has an 8.2% overall death rate. The second largest contributor to cancer-related mortality is HCC, which is the sixth most common malignancy in the world [1].

HCC is caused by the aggregation of many causes and the interplay of many systems. HCC develops and progresses as a result of a variety of mechanisms, including deactivated tumor suppressor genes (like p53), aberrant oncogene activity (like K-ras), dysregulated signaling pathways (like PI3K and MAPK), and epigenetic events (like microRNAs). Even more, HCC's progression could also be aided by exosomes that are able to deliver a huge number of protumorigenic chemicals [2].

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There are several risk factors considered to be associate with HCC. With ageing, the impact of male sex on the development of HCC reduces while that of alcohol use and HCV increases. Moderate alcohol use over a lifetime may result in HCC in the elderly. Study has also shown that the risk could be raised with smoking.

Regardless of infection of viral hepatitis, HCC risk could also be increase among patients with diabetes regardless of the existence of cirrhosis [3].

1.2. HCC related complications

Consequently, the formation of HCC can not only cause alimentary canal diseases but also malignant pleural effusion (MPE), which is a frequent complication among cancer patients, and can result from the growth of HCC, as well as digestive system problems. Cancer cells can be found in the fluid around the lungs in pleural effusions that are malignant. This shows that the illness has spread and that the patient has a shorter life span. Depending on the stage and type of cancer, individuals with malignant pleural effusion typically survive 4 to 7 months on average [4].

Additionally, varices in the esophagus or stomach can result from portal hypertension. Upper gastrointestinal bleeding (UGIB), a frequent side effect of HCC, may result from this. The tumor's potential for spontaneous rupture, which might cause more internal bleeding, is a major potential issue. Sudden abdominal discomfort, fullness, or hemodynamic instability are signs of spontaneous tumor rupture. Dynamic computed tomography (CT) can be used to detect this condition since it can identify HCC by its projecting shape, localized liver surface discontinuity, and perihepatic or intraperitoneal hemorrhage [5].

1.3. Screening

Early detection has been demonstrated to increase HHC patients' chances of survival. It is advised to get a checkup every six months because tumors frequently double in size every three to five months. When the estimated yearly risk of HCC for hepatitis C patients exceeds 1.5% and for hepatitis B patients exceeds 0.2%, surveillance is deemed to be cost-effective. Patients with cirrhosis who satisfy certain requirements must have an HCC evaluation. Radiological methods including magnetic resonance imaging (MRI) with contrast, multiphase computed tomography (CT), and ultrasonography are frequently used in HCC screening.

A better understanding of the hazardous disease could have positive implications for the development of more effective treatments which are severely needed [6].

2. Hepatocellular Carcinoma (HCC) Versus Other Cancers: A Focus on Prevention and Treatment Mechanisms

2.1. An Overview of HCC and Its Unique Challenges

Hepatocellular carcinoma (HCC) stands as a unique entity among malignancies, not merely as a matter of semantics but fundamentally in how it originates, progresses, and responds to therapeutic interventions. Originating from the hepatocytes, the main cell type in the liver, HCC is often the tragic finale of a sequence of liver diseases that may include hepatitis, cirrhosis, and fibrosis. This continuum of pathology sets the stage for HCC and offers both opportunities and challenges for prevention and treatment.

Unlike many other cancers, HCC often arises in an organ that is already compromised. This complicates the treatment landscape as therapies must not only target the cancer cells but also navigate an altered, often hostile, hepatic terrain.

Prevention strategies for HCC often intertwine with the management of these precursory liver diseases. Antiviral therapies for hepatitis, lifestyle modifications for alcoholic liver disease, and metabolic interventions for fatty liver disease are preventative measures that indirectly reduce the risk of HCC [7]. But even with these preventative measures, HCC has a propensity for late-stage diagnosis,

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partly because the liver is a remarkably stoic organ, capable of performing its functions even when significantly compromised.

The mechanism of tumorigenesis in HCC also differs from other malignancies. In most cancers, a single genetic mutation often triggers the uncontrollable growth of cells. In HCC, it's not always a straightforward one-gene, one-problem scenario. Epigenetic changes, oxidative stress, and chronic inflammation play pivotal roles in HCC pathogenesis, making it more complex and multifactorial.

When it comes to treatment, HCC is often less responsive to conventional therapies like chemotherapy and radiation. This is partly because the liver has a unique detoxifying role, capable of metabolizing and inactivating many pharmacological agents. Even targeted therapies, which have been revolutionary in the treatment of cancers like breast cancer and melanoma, often have reduced efficacy in HCC.

Emerging treatments such as immunotherapy offer some promise. Programmed cell death portion 1 (PD-1) blockade therapy, a form of immunotherapy, has shown promise in treating HCC [8]. However, not every patient responds to this form of treatment, a challenge that clinicians and researchers are still grappling with.

Comparative Mechanisms of Prevention and Treatment in HCC and Other Cancers

In the realm of cancer research and treatment, hepatocellular carcinoma (HCC) exists as an enigmatic character, often defying the norms established by other forms of malignancy [9]. When we venture into the landscape of prevention and treatment mechanisms across different cancer types, the unique challenges and opportunities presented by HCC become more evident.

First, let's examine the prevention paradigms. In breast cancer, for example, regular screening through mammography is the cornerstone of early detection. Similarly, in colorectal cancer, routine colonoscopy serves a similar purpose. These screening methods have the primary advantage of detecting cancers at an early stage, where curative treatment is most likely to be successful. However, HCC is often diagnosed at an advanced stage due to the lack of specific symptoms and effective screening methods [10]. While alpha-fetoprotein (AFP) levels and liver ultrasound are sometimes used for screening, their sensitivity and specificity are not universally reliable. This lack of effective screening options puts HCC at a preventive disadvantage, necessitating more aggressive treatment approaches when finally diagnosed.

In lung cancer, the most impactful preventive measure is smoking cessation. Likewise, in skin cancer, avoiding excessive sun exposure and using sun protection are key preventive strategies. In contrast, HCC prevention often revolves around controlling the underlying liver disease. Hepatitis B vaccination, antiviral treatment for hepatitis C, and lifestyle interventions to mitigate alcoholic liver disease or fatty liver are all routes to minimizing the risk of developing HCC. These strategies are not just preventive for HCC but are also essential for maintaining liver health, illustrating the interconnectedness of liver diseases and HCC [11].

Moving onto treatment mechanisms, HCC presents a conundrum. Traditional chemotherapy, a mainstay treatment for many cancers, often proves less effective in HCC. The liver's detoxifying capabilities, while essential for metabolic health, become a double-edged sword, metabolizing chemotherapy drugs and reducing their efficacy [12]. This pharmacokinetic challenge necessitates the exploration of alternative treatments. Targeted therapies, which have shown promise in malignancies like breast cancer with drugs like trastuzumab targeting HER2/neu receptors, face similar roadblocks in HCC. The heterogeneity of HCC tumors, with multiple signaling pathways implicated, makes it difficult to find a 'one-size-fits-all' targeted therapy.

On the brighter side, immunotherapy has been making strides in the realm of HCC treatment. Programmed cell death portion 1 (PD-1) blockade therapy, a form of immunotherapy, has shown promise. While traditional treatments often have the drawback of harming healthy cells along with cancerous ones, immunotherapy aims to empower the body's immune system to target cancer cells selectively. However, the efficacy of PD-1 blockade therapy in HCC is still under investigation, as not all patients respond to this treatment [13]. This necessitates a personalized medicine approach, a frontier that is being aggressively explored.

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While the treatment of other cancers often involves a multi-disciplinary approach involving surgery, chemotherapy, radiation, and targeted therapy, the treatment of HCC necessitates an additional layer of complexity. The underlying liver disease often requires simultaneous management, sometimes making liver transplantation the only viable option for both treating the cancer and addressing the compromised liver function.

To sum it up, the mechanisms of prevention and treatment in HCC stand apart from other cancers, rooted in the uniqueness of its pathophysiology and the complexity of the liver environment in which it exists. While other cancers have benefited from advances in early detection and targeted therapy, HCC lags in these areas but offers new avenues for exploration, particularly in the realm of immunotherapy.

2.2. Treatment Mechanisms in Other Cancers

Before plunging back into the depths of hepatocellular carcinoma (HCC), it's instructive to pause and consider how other cancers are generally approached in terms of treatment. This interlude serves to further highlight the unique challenges and opportunities presented by HCC and offers a backdrop against which its distinctiveness can be more vividly understood.

When we talk about other cancers, such as breast cancer, lung cancer, or melanoma, the treatment protocols often follow a somewhat predictable pattern—surgery for localized disease, chemotherapy for systemic control, radiation for localized but inoperable tumors, and increasingly, targeted therapies and immunotherapies for specific subtypes [14]. However, the effectiveness of these treatments varies widely across cancer types, largely due to our understanding of their molecular and genetic underpinnings.

In breast cancer, for example, hormonal therapies like tamoxifen or aromatase inhibitors are effective in tumors that express estrogen or progesterone receptors. In contrast, Herceptin targets HER2-positive breast cancer cells, leaving other cells largely unharmed [15]. This kind of targeted therapy has revolutionized breast cancer treatment but is a luxury not yet fully afforded to HCC, primarily due to its heterogeneous nature and the complexity of underlying liver diseases.

Lung cancer, too, has seen significant advances in treatment. Small molecule inhibitors like erlotinib target epidermal growth factor receptor (EGFR) mutations, providing another example of targeted therapy. Immunotherapies, particularly checkpoint inhibitors that target PD-1/PD-L1 pathways, are showing promise in treating lung cancer, especially in patients who don't respond to traditional chemotherapy [16].

Melanoma, once considered almost universally fatal in its advanced stages, has been dramatically transformed with the advent of immunotherapies like ipilimumab, which targets CTLA-4, and pembrolizumab, which targets PD-1. These treatments have turned melanoma into a more manageable disease and have significantly extended survival rates for many patients.

Colorectal cancer, another major malignancy, often involves a combination of surgical resection followed by chemotherapy. Newer targeted agents like bevacizumab, which inhibits angiogenesis, are also being incorporated into treatment regimens, offering improved outcomes [17].

As we reflect on these advancements in cancer treatment, it becomes clear that much of the progress hinges on an ever-deepening understanding of cancer genetics and immunology. Yet, this personalized, targeted approach is still in its infancy in HCC. The heterogeneity of the disease, the often-compromised liver in which it occurs, and the multifactorial etiology involving viral infections, lifestyle factors, and metabolic diseases make HCC a more elusive target for both prevention and treatment.

The dichotomy between the treatment landscapes of HCC and other cancers is evident. While recent years have seen exponential growth in the targeted and immune-based therapies for many cancers, HCC remains a challenging frontier. This challenge is not just scientific but also clinical, as treating HCC often involves managing not just the tumor but also the underlying liver disease, adding layers of complexity seldom encountered in other malignancies.

With this comparative perspective in mind, we can now refocus on HCC, particularly looking into the latest advancements in its treatment, which offer a glimmer of hope in an otherwise challenging landscape.

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3. Recent Management

3.1. Transarterial Chemoembolization (TACE)

Transarterial Chemoembolization (TACE) is the first-line therapy for HCC in the intermediate stage, in accordance with Barcelona Clinic Liver Cancer (BCLC) staging. TACE is crucial for both early and late stages of HCC. TACE had corresponding 1-year, 3-year, 5-year, and 8-year survival rates of 93.4%, 75.4%, 63.1%, and 51.1%. TACE is the first-line therapy for around 50% of BCLC-C HCC patients receiving real-world clinical care [18].

The TACE therapy approach is a very powerful way against cancers. The microcirculation of the tumor embolizes when chemotherapy is administered by a catheter placed into the artery delivering blood to the afflicted region, producing a long-lasting cytotoxic impact. Chemotherapy becomes a less harmful alternative for patients because of this strategy, which lowers its total systemic toxicity.

This therapy method's applicability for liver-related conditions is a major benefit. TACE and other treatments can be used to target the afflicted region while protecting healthy liver tissue from ischemia since the liver has two blood supply, from the hepatic artery and portal vein. This operation is crucial for ensuring the patient's general health and wellness since it treats the tumor while maintaining the patient's healthy liver tissue. TACE and arterially directed treatments in general provide the potential to preserve healthy liver tissue from ischemia.[19]

The two distinct forms of TACE procedures are drug-eluting bead-based TACE (DEB-TACE) and conventional TACE (cTACE). In cTACE, following the administration of cytotoxic drugs like doxorubicin, epirubicin, mitomycin, or cisplatin, chemotherapy and embolic fragments are supplied via the injection of lipoalcohol, an oiling radioactive opaque substance. Contrarily, DEB-TACE employs chemotherapy-loaded, non-resorbable embolic microspheres. The agent can be continuously released from these microspheres. There is still disagreement about which approach is better than the other. In terms of full response rate and overall survival rate, DEB-TACE performs better than cTACE, according to Zou et al.'s meta-analysis. However, when it comes to serious side effects, there is no statistically significant difference between the two regimens.[20]

3.2. Combination therapy

TACE combination therapy alternatives include radiofrequency ablation (RFA) and microwave ablation (MWA). RFA causes heat-based thermal cytotoxicity by the use of a needle electron. Once the temperature rises to between 60 and 100 degrees Celsius, instant thermocoagulation necrosis can occur.

Regarding the viability, RFA is more successful in treating lesions that are approximately 3 cm in size, however owing to the heat-sink effect, it may not be useful for tumors positioned close to big arteries.

High-frequency electromagnetic radiation is used in the MWA procedure to induce coagulation necrosis. MWA is more effective in heating target lesions than RFA. Additionally, the heat-sink effect has less of an impact on its efficacy. The larger ablation zone makes it possible for MWA to treat bigger tumor.

TACE is regarded as a generally safe procedure, however, few unfavorable incidents have been noted. TACE may have ischemia-related side effects, including liver and biliary damage, pancreatitis, cholecystitis, bile duct necrosis and cholecystitis. The results suggest that TACE may have a high failure rate. Nevertheless, according to current research, depending on their stage, not all BCLC patients can benefit from TACE [21].

3.3. Radiation therapy

Transarterial radioembolization (TARE) and Stereotactic radiotherapy (SBRT) are two types of radiation treatment.

In contrast to other embolizing treatments like trans-arterial chemoembolization (TACE), radioembolization has no macroembolic effect. Therefore, neither the therapeutic benefits nor the potentially dangerous side effects of the operation are determined by any ischemic impact but rather by

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the radiation carried by the microspheres. Candidates for TARE must have unresectable HCC and a minimum three-month survival expectation; those with a high tumor burden or compromised liver function are not eligible [22].

By applying greater fractional doses of radiation in fewer fractions, stereotactic body irradiation (SBRT), a kind of external beam radiotherapy, differs from conventional radiotherapy and can achieve local control of HCC lesions of up to 90%. According to research by the Cong team, SBRT has a tolerable level of toxicity and a good local control rate. In 4-6 SBRT regimens, a modest dosage seems to provide manageable toxicity. 9.8% of instances include grade 3+ toxicity, whereas 3.9% involve grade 5 toxicity. The data suggest that SBRT may provide tumor patients with a palliative choice [23].

When utilized in HCC patients who are difficult to treat with existing therapy, SBRT has the potential to improve the prognosis. Since RFA is contraindicated for tumors close to the main arteries or the hilum, SBRT is a useful option for RFA in cases when malignancies are close to the diaphragm.

3.4. Chemotherapy

Chemotherapy is a form of systemic therapy that eliminates cancer cells by using anti-cancer (cytotoxic) medications. Typically, a syringe is used to inject these medications straight into a vein, or the tablets are swallowed.

Systemic chemotherapy may be used to treat cancers that spread normally through the circulation, which is how cancer cells move throughout the body. This aids in the patient's recovery and decreases the risk of cancer recurrence [24].

3.5. Immunotherapy

Navigating the intricate labyrinth of hepatocellular carcinoma (HCC) treatment is akin to sailing uncharted waters, full of unpredictable currents and hidden obstacles. However, even in such challenging terrains, the medical community is making headway, propelled by innovative research and technological advancements [25]. As we've already explored the intricacies and unique challenges of HCC in comparison to other cancers, it's time to delve into the latest advancements that are changing the outlook for HCC patients.

One of the most talked-about strategies in HCC treatment currently is immunotherapy, specifically checkpoint inhibitors like Programmed Cell Death Protein 1 (PD-1) and its ligand PD-L1. These molecules have a role in suppressing the immune response, which cancer cells exploit to evade detection. Drugs like nivolumab and pembrolizumab are PD-1 inhibitors that have shown promise in early clinical trials. But here's where HCC introduces its characteristic complexity—while some patients respond remarkably well, others show no response, and the reasons for this variability remain elusive [26]. Researchers are now focusing on identifying biomarkers that can predict treatment response, which is vital for personalizing treatment plans.

3.6. Targeted therapies, locoregional therapies and gene therapies

Another exciting area of HCC research involves targeted therapies. Sorafenib, a multi-kinase inhibitor, was among the first targeted therapies approved for HCC and remains the standard first-line treatment. However, its efficacy is often limited by drug resistance. Newer agents like lenvatinib are being tested as alternative first-line treatments. The FGF19-FGFR4 signaling pathway, implicated in HCC pathogenesis, is another potential target, and drugs inhibiting this pathway are in various stages of clinical development.

The realm of locoregional therapies is also expanding, offering new tools in the armamentarium against HCC. While surgical resection and liver transplantation remain the most definitive treatments, they are often reserved for early-stage disease.

Then there's the burgeoning field of gene therapy, which aims to correct or replace faulty genes contributing to HCC development. While this is still largely experimental, early results show promise, particularly with the use of CRISPR-Cas9 technology to edit specific genes implicated in HCC [27].

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Coupled with advancements in sequencing technologies that allow for more comprehensive profiling of HCC tumors, gene therapy could offer an entirely new avenue for treatment in the future.

Another innovative approach is the use of liquid biopsies for early detection and monitoring. This involves the analysis of circulating tumor DNA (ctDNA) in the blood, offering a minimally invasive method to gauge treatment response and predict recurrence [28]. While still in the research phase, liquid biopsies have the potential to revolutionize HCC monitoring, particularly in patients with underlying liver diseases where traditional biopsy is risky.

As we stand on this new horizon of HCC treatment, the future seems less bleak than before. The advancements in immunotherapy, targeted treatment, locoregional therapies, and experimental strategies like gene therapy are not just incremental improvements but paradigm shifts that hold the promise of transforming HCC from a near-certain death sentence to a manageable condition [29].

In conclusion, the unique challenges posed by HCC, stemming from its complex etiology, late diagnosis, and the often-compromised state of the liver, necessitate innovative approaches to both prevention and treatment. While we have much to learn, particularly in making treatments more universally effective, the rapid advancements in medical science provide a reason for cautious optimism.

4. CircRNA-LNP therapeutic vaccine: An Outlook

Although the implantation would facilitate liver function properly, finding a suitable liver to implant for advanced HCC patients is complex and usually not affordable. HCC is a costly disease for patients and healthcare systems, particularly in low-income countries with limited resources. Therefore, effective and cost-efficient treatment is necessary.

There are preventative vaccines commercially available, however, there is a lack of therapeutic vaccines for HCC. HCC is a type of cancer caused by inflammation. Thus, clinical statistics suggest that an immunotherapeutic approach may be effective as a candidate treatment for HCC patients, improving their prognosis.

We here propose an innovative strategy of therapeutic vaccine utilizing circRNA over mRNA with LNP to treat Hepatocellular Carcinoma Cancer (HCC) which harnesses the advantage and function of both circRNA and LNP.

4.1. LNP part

A circRNA could be a remedy for naked mRNA's inherent instability and susceptibility to nuclease degradation and self-hydrolysis. It is more resistant to exonuclease degradation and more stable than linear mRNA. Wesselhoeft RA et al.'s recent research has demonstrated that circRNA and lipid nanoparticles may coexist. When encapsulated by LNP, LNP shields the circRNA from extracellular ribonucleases, providing two layers of insurance and aiding intracellular circRNA transport [30].

4.2. LNP part: Advantages of using LNP as a drug delivery platform

LNP-circRNA platform is a complex multi-component system, every distinct part and component serves a unique purpose in functioning as an effective carrier for RNA drugs.

We will now discuss the benefits of LNP and the component factors that influence them.

The ionizable lipids composed of the LNP head group are essential because of their positive charge and size.[30]

Holding back unfavorable interactions with cell membranes can improve the stability of LNPs. Furthermore, disrupting the endosomal membrane can help enhance the endosome escape. Encapsulation and delivery efficiency to nucleic acid cargo are also promoted at typically > 90% across nucleic acid modalities due to the ionizable lipids.

PEG-lipids are also crucial in the composition of LNP, which mainly participates in LNP formation. The hydrophilic steric barrier on the LNP surface made up of PEG-lipids, controls the size, bioactivity, and stabilizes LNPs by aiding lipid nano-particals self-assembly. PEG-lipids can also help decrease interactions with serum proteins and prevent LNP from phagocytosis to a certain degree. This can improve the EPR effect by increasing the circulation cycle and enables tiny LNP to preferentially

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accumulate in tumor tissue. By inhibiting the fusion or aggregation of LNP particles, one can also increase spatial stability. By doing this, PEG-lipids extend the blood's circulation time, which leads to increased drug accumulation at the target location [31].

It was found that LNP containing 5% PEG-lipids had a higher rate of tumor accumulation than LNP containing 2.5% PEG-lipids [33]. To improve the efficiency of delivering nucleic acid, a monomolecular phospholipid layer of LNP is made utilizing neutral phospholipids. This layer aids in cell stabilization and binding. Despite creating a layer, phospholipid endosomes have a variety of activities, including cargo distribution and effective encapsulation [34].

For the purpose of being a reliable drug delivery platform, stability is crucial. There are extra factors that govern the stability of LNPs. Cholesterol improves particle stability by regulating the fluidity of membranes. To achieve certain target site accumulation, stopping the phagocytosis of the particles, the positively charged carrier must be shielded from the non-specific interactions with serum proteins [34].

4.3. LNP part: liver targeting

Targeting is classified into passive targeting and active targeting. Passive targets the liver through physical properties, while active uses a specific ligand that binds to receptors in the liver's targeted cells.

Passive targeting of LNPs is crucial in vaccine design. Utilizing combinatorial techniques, a novel class of phospholipids known as multi-tailed ionizable phospholipids (iPhos) has been synthesized. In iPhos, an amine group and a brief hydrophobic acid group connecting fragments are combined. It is suggested that in formulation nucleic acids are preferentially delivered to the liver, negatively charged phosphate groups promote membrane fusion and induce endosomal escape [33].

One of the elements of the biomolecular corona that influences the transport of nucleic acids via LNP is apoE. Since liver cells mostly generate and are the most abundant source of apoE, the liver is frequently the final destination of intravenous LNP [32]. The organic targeting of lipid nanoparticles is determined by the joining groups of lipid compounds. The O-series of ester bonds are selected in order to allow the joining groups of lipid compounds to target the liver.

Generally speaking, particle surfaces can be altered by specific ligands that bind to receptors on specific types of target cells or by changing their chemical composition, thereby altering biodistribution and achieving chemical targeting. This can guarantee targeted distribution to certain tissues or cells and prevent the accumulation of off-target regions [33].

4.4. CircRNA part: Advantages of utilizing circRNA over conventional mRNA

By varying splicing, exon or intron cyclization, or a combination of the two, pre-mRNA generates Circular RNAs (circRNAs), a separate type of single-stranded circular RNA molecules. Due to the absence of the 3' poly A and 5' cap structures, which make it more difficult for exonuclease to digest, it is more stable than linear mRNA [35].

Moreover, when combined with soluble protein, circRNA can also act as a potent adjuvant which is crucial in enhancing the effectiveness of vaccines.

Recent studies show that certain types of circRNA can provide greater clinical benefits than traditional mRNA. Lipid nanoparticles, specifically those using the ionizable lipidoid cKK-E12, have been found to effectively deliver circRNA in living organisms. Purified hEpo circRNA encapsulated in LNPs showed strong expression compared to 5moU-mRNA in 293 cells. When injected into adipose tissue, LNP-circRNA showed a slower decay in serum hEpo levels compared to LNP-5moU-mRNA [30].

It is currently possible to use circRNA-LNP as a therapeutic vaccine component due to its proven clinical specificity and LNP combination benefits.

Effective cancer treatments should circulate in the bloodstream, accumulate at high levels in tumor sites, penetrate deep into tissue, and disrupt metabolic pathways. Active targeting is more efficient and carries less risk of non-specific interactions and drug resistance. Specific ligand-receptor binding promotes selective drug accumulation in target cells and organelles [36].

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4.5. Some antigens and membrane proteins that could possibly be targeted in the design of an LNP-circRNA vaccine for HCC.

Anti-HER2, OX40L, proinflammatory cytokines (such as IL-12, IFN-α, granulocyte-macrophage colony-stimulating factor, and IL-15), IL-23, IL-36$\boldsymbol{\gamma}$, are antigens or proteins have superb abilities to trigger the body's immune response and block tumor progression or eliminate tumor cells.

The combination of the above-mentioned LNP passive targeting of the liver and the active targeting antigens or membrane proteins, which are specifically present on the surface of the hepatocellular carcinoma tumor, will give double insurance [37].

4.6. Besides, the engagement of combination therapy plays an essential role in cancer vaccine therapy.

4.6.1. Cemiplimab: Cemiplimab is a monoclonal antibody that targets PD-1 selectively. It works by the binding of PD-1, which causes the inhibition of cancer cells on T cells to be released. Therefore, T cell receptor signaling is reactivated, restoring anti-tumor activity and boosting the immune system's capability to kill cancer cells. Finally, this has a potent anti-cancer impact [38].

4.6.2. BNT131: Increasing the amounts of the cytokines IL-12sc, IL-15sushi, IFN, and GM-CSF in the tumor microenvironment by the use of mRNA may improve the immune system's capacity to combat cancer cells, offering a potential route toward developing secure and efficient cancer treatments [39].

5. Conclusion

HCC is a unique form of cancer that primarily originates from hepatocytes in the liver. It often occurs in livers that are already compromised due to conditions like hepatitis, cirrhosis, or fatty liver disease. This poses unique challenges for both prevention and treatment, as interventions must navigate a complex, compromised hepatic environment.

Treatment of HCC is complicated by the liver's ability to metabolize and inactivate many therapeutic agents, making traditional chemotherapy often less effective. Targeted therapies, effective in other cancers, find limited success in HCC due to tumor heterogeneity and multiple implicated signaling pathways. Unlike other cancers that benefit from a multidisciplinary approach involving chemotherapy, radiation, and surgery, HCC requires an added layer of complexity—managing the underlying liver disease. Recent advancements in HCC treatment are promising. Immunotherapy, particularly PD-1 inhibitors like nivolumab and pembrolizumab, have shown varying levels of success. Targeted therapies like Sorafenib remain standard but face issues of drug resistance. New techniques like stereotactic body radiation therapy (SBRT) and experimental fields like gene therapy and liquid biopsies are emerging as future avenues for HCC treatment.

The harness of the therapeutic vaccine to HCC still warranted explosion. We've presented our unique idea of circRNA-LNP therapeutic vaccine towards the aspects of carrier and nucleic acid, which combines the benefits of both circRNA and LNP, will be innovatively efficient in cargo delivery and encapsulation, yet more stabilized. However, cross-over issues still need to be further considered.

To summarize, HCC presents unique challenges and opportunities in the realms of prevention and treatment. Its complex etiology, compromised hepatic environment, and late-stage diagnosis require innovative approaches. While there's much to learn, particularly in making treatments universally effective, advancements in medical science provide cautious optimism for the future of HCC management.

6. Authors contribution

All the authors contributed equally and their names were listed in alphabetical order.

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