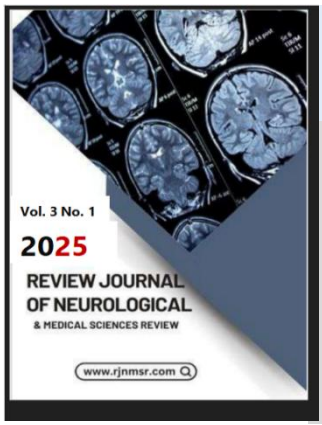

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Role of Alpha Feto Protein (AFP) in the Tumor Microenvironment (TME) of Hepatocellular Carcinoma (HCC)

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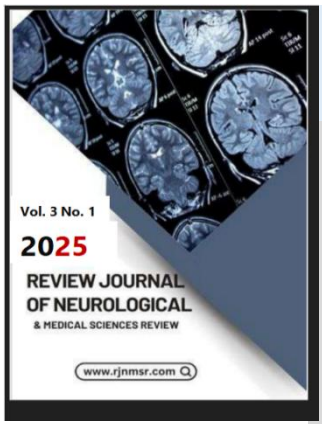
Abstract
The present study is aimed at exploring the anti-tumor effects of PDI on HCC and the underlying molecular mechanism as well functions associated signalling pathway for specific cancer diagnosis. Tumor microenvironment (TME) is actually a key factor underlining the development and progression of HCC. As for the conventional serum biomarker, Alpha-Fetoprotein (AFP) which has been long used for HCC diagnosis and prognosis, its function has gradually been found not only as a passive biomarker, but also as an active player in regulation of the TME. This review aims at identifying the various functions of AFP in the context of the TME of HCC, particularly on tumor growth, angiogenesis, immune regulation and differentiation and metastasis. The review also analyses some of the clinical aspects of AFP in HCC such as the therapeutic potential of AFP and its ability to predict the effectiveness of treatments. Newer studies on other novel biomarkers associated with AFP and genetic aspects of the function of AFP in TME are presented and future strategies in AFP-directed therapies further elaborated. Elucidating the multifaceted nature of the relationship between AFP and TME will be crucial for designing the new therapeutic approaches that can enhance the HCC diagnostics and treatment.



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Keywords: Alpha-fetoprotein (AFP), Hepatocellular Carcinoma (HCC), Tumor Microenvironment (TME), Liver Cancer, Tumor Biomarkers, Immunomodulation, Cancer Prognosis, AFP Signaling Pathways, Tumor Invasion, Cancer Metastasis, Liver Tumor Immunology, Hepatic Oncology, AFP and Immune Evasion, AFP as Diagnostic Marker, Tumor Angiogenesis

Introduction

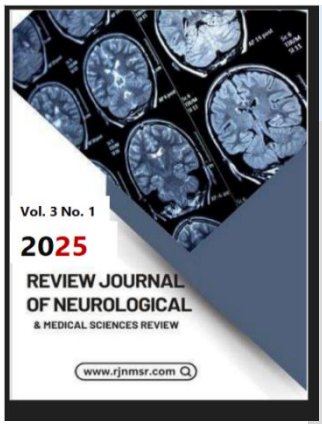
Hepatocellular carcinoma (HCC) is the most common primary cancer originating from the liver; it is a global public health issue because of the disease's high incidence and mortality. However, for patients diagnosed with HCC, there is still a poor outcome on treatment especially at the later stage. The tumor microenvironment (TME) is considered to be an essential factor of cancer initiation, advancement, and also drug resistance. In this complicated context, Alpha-Fetoprotein (AFP), which is a biomarker widely studied for HCC, has recently become the focus of interest for its roles beyond the diagnostic one. Thus, this review will further discuss the complex involvement of AFP in the context of TME in HCC with regards to its contribution in tumor growth, immune escape, and possible treatment strategy.

Hepatocellular Carcinoma HCC

HCC is the fifth most common cancer worldwide and the third top cause of cancer mortality (Bray et al. , 2018). The development of HCC is causal with main predisposing factors being the infections with hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, alcoholism and non-alcoholic fatty liver disease (NAFLD). The factors that lead to the development of HCC are numerous and multifactorial and include chronic infection and inflammation, liver cirrhosis and genetic mutations (El-Serag, 2011), (Jabeen et al., 2025). Current diagnostic approaches to HCC consist of imaging, liver biopsy, and serum markers: AFP's sensitivity and specificity are usually low, however (European Association for the Study of the Liver, 2018). HCC being a malignant cancer is treated through different ways based on the stage of the disease; through surgery, liver transplantation, regional therapies, and through molecular therapeutics, tyrosine kinase inhibitors and immune checkpoint inhibitors.

Molecular Subtype of HCC

The TME in HCC is a complex structure formed by cancer cells, non-neoplastic stromal cells, immune cells, ECM, and cytokines and growth factors (Whiteside, 2008). These components work together to promote tumor development, angiogenesis, immune escape, metastasis and invasion (Hanahan & Weinberg, 2011). In HCC, the TME is especially determined by the presence of chronic liver disease, which provides an inflammatory backdrop for initiating and advancing the tumor (Coulouarn & Clément, 2014). Tumor-associated immune cells such as TAMs, Tregs, and MDSCs are immunosuppressive and help the tumors evade immune system and escape therapy (Kuang et al. , 2010) , it was crucial to identify the TME function in HCC and consider



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the tumor stroma and immune factors in the attempt of devising new therapeutic approaches.

Alpha-Fetoprotein (AFP)

Historical Aspect

AFP which is a glycoprotein found on the fetal liver, yolk sac and gastrointestinal tract is onco fetal protein that is re-expressed in HCC in most cases as elucidated by Abelev in 1971. AFP was first discovered in the 1960s and soon the significance of AFP as a biomarker for HCC, particularly in individuals with high likely hood for development of CLD was discredited by previous workers. However, AFP is of limited use as a diagnostic marker; the diagnosis is early-architecture HCC in 30–40% of cases have AFP levels within the normal range (Trevisani et al. , 2001). Nevertheless, AFP continues to be an essential part of HCC diagnosis; it frequently is employed in conjunction with other diagnostic modalities. In addition to using AFP as a diagnostic/surveillance marker, the attention of the scientific community these last years has shifted towards the function of this protein within the Tumor Microenvironment (TME), and notably that of a “messenger/pro-angiogenic, immunomodulatory tumor alkalinizing glycoprotein”.

Review

Role of AFP in Tumor Microenvironment (TME) AFP Expression in HCC TME

Mechanisms and Patterns

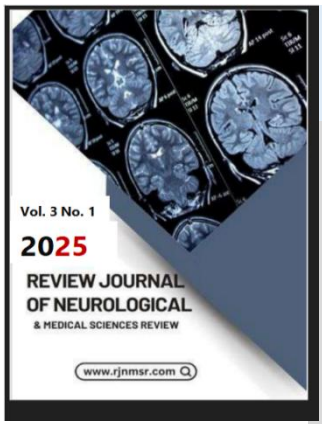
AFP is widely expressed in HCC tissues, and the expression is positively related to the tumor size, differentiation, and invasiveness (Nakabayashi et al. , 2012). In TME, AFP may upregulate or down regulate different cellular events such as cell proliferation, cell death, cell migration etc. The regulation of AFP in HCC consists of many pathways and one common characteristic of HCC, which is the Wnt/β-catenin pathway, that has been shown to cause the up-regulation of AFP (Kaseb et al. , 2009). Moreover, hypoxia in the TME, which often accompanied by rapidly growing tumours, is capable to enhance expression of AFP via binding with HIFs (Li et al. , 2011).

Influence of AFP on Modulation of Immune System in TME

There is a significant impact of AFP on the formulation of immune system of HCC. Obviously, it can suppress the function of DC and the occurrence of antigen presentation, which in turn decreases the anti-tumor T cells response (Li et al. , 2014), (Akbar et al.). AFP can also expand immunosuppressive cell populations like Tregs and MDSCs which further reciprocal for the capacity of immune system to identify and kill cancer cells (Wang et al. , 2013). These actions help in writing a immunosuppressive environment that hampers the immune action of T cells and permits HCC to proliferate.

AFP and Angiogenesis in HCC

Angiogenesis is the process of growth of new capillaries from existing one it is one of the characteristics of lot of cancers due to metabolic requirement for nutrients and oxygen for the growing mass of tumor (Folkman, 2002), (Ammar Mehfooz et al.). AFP has also



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been suggested to play a role in tumour angiogenesis in the HCC TME. Some investigations have ascertained that AFP can increase the intensity of VEGF that plays a crucial role in angiogenesis which means that new blood vessels providing nutrients and support for tumor and metastases formation are developed (Tian et al. , 2016), (Khalid et al., 2024). This pro-angiogenic effect of AFP can be adduced to the fact that AFP has been implicated into the aggressiveness of HCC and can be targeted for anti-angiogenic therapy. AFPs speculated to have interaction with Cancer-Associated Fibroblasts (CAFs), a key constituent of the TME is involved in the ECM changes, tumor support with promotion of metastasis (Kalluri, 2016), (Safdar et al., 2022).

Several reports have provided evidence that CAFs in the HCC TME are modulated by AFP to varying extents of activation and functionality. For example, AFP may promote the production of matrix metalloproteinases (MMPs) of CAFs as a result of which the ECM is degraded making tumor invasion and metastasis possible (Shang et al. , 2018), (HUSNAIN et al.). The reciprocal interaction between AFP and CAFs fosters HCC cells to invade the surrounding areas and spread to the distant organs thereby promoting the general poor prognosis linked with HCC.

Role of AFP in HCC Metastasis

TME Perspective

Metastasis is the principle cause of cancer related mortality in HCC, and AFP is a gradually appreciated determinant. Constitutively, in the TME, AFP can promote invasive phenotypes in HCC cells through changes in multiple cell signaling pathways related to EMT, which is vital to metastasis (Liu et al. , 2015), (ZHAIRA et al.). AFP can stimulate the PI3K/Akt signaling cascade which results in upregulation of mesenchymal markers and down regulation of epithelial markers thus enhancing the procedure of EMT and metastasis (Geng et al. , 2012). AFP itself can bind integrin and other CAMs, which may affect adhesive characters of HCC cells and promote their extravasation from the primary tumour mass (Liu et al. , 2014).

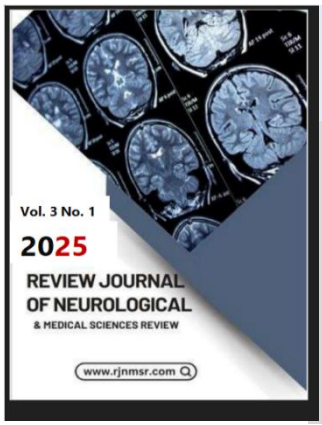
AFP and Immune Evasion in HCC

Mechanisms of Immune Evasion in HCC TME

In fact, immune evasion is one of the major properties of cancer that permit the tumour cells to go unnoticed by the immune system and progress (Hanahan & Weinberg, 2011). In HCC, the TME is closely attached to such a process, and AFP bears great significance in it. AFP interferes with the activation and function of T cells, natural killer (NK) cells, as well as DCs; thus, play a role in immune evasion (Tian et al. , 2012). This immunosuppressive effect is achieved by several mechanisms, including the promotion of the inhibitory cytokines, the TFG-β and IL-10 that suppress anti-tumor immune reactions (Li et al. , 2014).

Functions of AFP Regarding Immune Check Points

Since immune checkpoint are major controllers of immune responses including the programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated antigen



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4 (CTLA-4) these are often used by tumors as a survival strategy (Pardoll, 2012). Some of the immune checkpoints, which have been regulated by AFP within the TME of HCC have been described as follows: For example, AFP can enhance the production of the protein PD-L1 on malignant cells and MDSCs resulting in T-cell inhibition and immune tolerance (Zhu et al. , 2015). These findings suggest that the parallel between AFP and immune checkpoints may help improve the outcome of combining AFP-targeted therapies with immune checkpoint inhibitors in the presence of HCC.

The Effects of AFP on Immunosuppressive Cell Populations in the TME

Apart from regulating the immune checkpoints, AFP was also found to indirectly stimulate the development and functional activation of immunosuppressive cells in the tumor microenvironment. Both Tregs and MDSCs are important for immune tolerance and suppression of anti-tumor immunity, and AFP has been found to be highly relevant to their function (Wang et al. , 2013). AFX promote the expansion of Tregs and MDSCs, and boost their inhibitory actions, and hence, induce an immunosuppressive TME that fosters tumor growth and survival (Li et al. , 2014). This is evidenced by a tener of tarting to expand and promote immunosuppressive cells while on the other side suppresing effector immune cells as portrayed by AFP in the immunoevasion of HCC.

Clinical Relevance of AFP in HCC TME

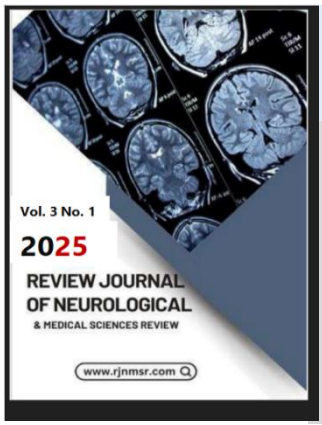
Current Role of AFP in Assessing HCC Survival and Therapeutic ResponseIn essence, AFP has been employed for many years as a prognostic index in HCC; elevated AFP is deadly in terms of survival (Tangkijvanich et al. , 2000). The involvement of AFP in the TME is also significant in controlling tumor response to treatment by: Jia et al. , Zhou et al. , have found out that if the concentration of AFP is soaring among HCC patients, then the reaction to conventional treatments, including surgery, TACE and systemic treatment such as sorafenib is less favorable.

Some of the reasons are that AFP acts within the TME as an immunosuppressive and pro-angiogenic factor that can hamper the prognosis of the tumor as well as decrease the effectiveness of anti-cancer treatments.

AFP-Targeted Therapies

Recent Investigations and Trials

Since, TME is intrinsic with poor prognosis and more significant the values of AFP, there is increased effort to identify AFP-directed therapies. One strategy is the use of AFP based vaccines; these vaccines are geared at making the patient's immune system identify HCC cells that have AFP on their surface as foreign and hence a target for destruction (Butterfield et al. , 2013). Auto antigen therapy on the other hand has some evidence of success in modulating immune response and improving prognosis of HCC patient though the evidence needs refinement (Greten et al. , 2010). Also, the use of nanoparticles conjugated with ant-fetal AFP antibodies to target drug delivery systems to HCC cells and reduce the toxicity of drugs to normal cells have been proposed (Wang et al. , 2016).



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AFP as an Indicator for the Efficiency of Introducing Immune Checkpoint Inhibitors:
Cancer has become a systemic disease that is treatable, in part, by immune checkpoint inhibitors, including HCC (El-Khoueiry et al. , 2017). Nevertheless, not all individuals with PDE4D and NK-1 receptors respond therapeutically to these therapies, and there is the need for a clinically valid biomarker for such therapy. New investigations reveal that AFP play the role of the marker for the effectiveness of the immune checkpoint inhibitors in the treatment of HCC Zhu et al. , 2018. Lower levels of AFP are associated with better response to PD-1/PD-L1 inhibitors possibly because of less immunosuppressive TME. These results raise the possibility of extrapolating that AFP is not only useful in predicting the prognosis but also in determining the decisions about immunotherapy for HCC.

Current Molecular Characterization of HCC and Trends in Precision Medicine

The use of NGS, NGS-based analysis of HCC has shown that there is great genetic diversity within the tumor, which impacts patients response to treatment. Future investigations of genomic classification of HCC tumours can help in establishing mutations that can describe therapeutic targets and, thus, make an individualistic approach to therapeutic therapy (Villanueva, 2019).

EZH2 Inhibitors and Epigenetic Targets

Polycomb repressive complex 2 (PRC2) component enhancer of zeste homolog 2 (EZH2) is often overexpressed in HCC and correlated with the patients' prognosis. Indeed, the use of EZH2 inhibitors has been proven effective in inhibiting growth of HCC through restoration of expression of tumor suppressor genes. EZH2 suppression might also improve the effectiveness of immune checkpoint inhibitors in therapy of HCC.

MET Inhibitors

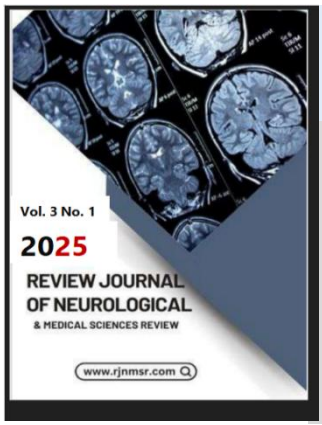
Several studies have shown that MET signaling pathway when overexpressed because of MET receptor or its activator HGF, plays a role in HCC progression. Tivantinib and cabozantinib which are MET inhibitors are being investigated in the treatment of MET positive HCC.

FGFR Inhibitors

Fibroblast growth factor receptor (FGFR) is involved in fundamentals steps in liver regeneration and fibrosis. Pemigatinib and futibatinib that belong to the FGFR inhibitors are under clinical trials for the usage in HCC patients with detectable FGFR aberrations.

Immune Modulation Through TME Targeting

The TME in HCC remains catabolic and consists of immune checkpoints such as Tregs and TAMs. Aiming at some TME elements, like CCR4 or CSF1R, in order to increase the efficacy of an immunotherapy in HCC.



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Liquid Biopsies

Other blood-based diagnosis and staging technique include circulating tumor DNA and circulating tumor cells in which liquid biopsies are useful in tumor kinetics, detecting MRD, and treatment response in HCC. It has potential in the best practice of personalized medicine in the management of HCC.

Molecular Subclassification of HCCC

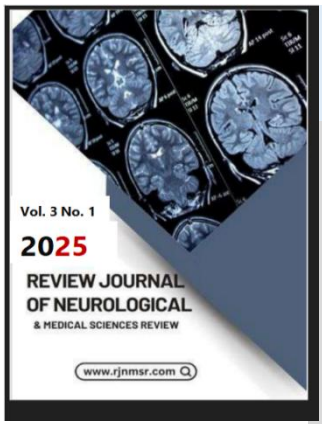
Molecular characterization has unveiled differed subtypes of HCC which exhibit different genetic alterations, immune environment, and sensitivity to treatments. This subclassification proves useful in biomedical research especially in the determination of the best treatment approach for the HCC. Combination Therapies: Fusion of TKIs or FGFR inhibitors with immune checkpoint inhibitors or epigenetic drugs will be the best way of overcoming resistance and enhancing poor prognosis rates of HCC. Current investigations under way include different regimens of combined therapies.

Emerging Research and Future Directions

Studies on the molecular biomarker function of AFP in HCC have proceeded beyond the marker function of AFP and discovered that there are other AFP related molecules which are potential biomarkers for disease and/or treatment. For instance, AFP mRNA and peptides derived from AFP are currently in scientific research studies as better biomarkers of HCC activity within the TME than AFP (Tsai et al. , 2017). Further, research is being carried in relation to AFP glycosylation profiles that could provide more information concerning the nature of the tumor and the outcome of the patient (Nakabayashi et al. , 2012). Recent studies in TME have employed modern molecular and genetic approaches to findings of the specific genetic and epigenetic controls of AFP in HCC. Due to the lack of therapeutic options, identification and comprehension of the molecular factors regulating AFP synthesis and its crosstalk with the TME are regarded as significant. For instance, the discovery of the microRNAs that target AFP could potentially open up new ways on how to manipulate AFP levels and its impact within the TME (Chen et al. , 2013). Further research on the signaling interactions between AFP and other cancer promoting pathways in HCC can identify new targets for combined treatments.

Future Development of AFP-Targeted Therapies

The future of AFP-targeted therapeutics will involve better approaches able to address the limitations that derive from the fact that AFP is both a biomarker and an active component of the TME. Thus, the concomitant use of AFP-targeted therapies with other systems including immune checkpoint inhibitors, anti-angiogenic agents and TME-modulating drugs may be potentially beneficial to enhance the therapeutic efficacy in HCC. In the same case, strategies such as the molecular characterization of the tumor and the TME as well as the AFP levels may help in selecting the right customized treatment regimens for patients with HCC.



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Conclusion

Therefore, AFP acts as a prognostic factor, as well as a promoter and a mediator of the hepatocellular carcinoma growth, immune escape, angiogenesis, and metastasis. In fact, despite the fact that AFP has been used and investigated in the context of diagnosis and prognosis of HCC, the data presented in the manuscript demonstrates an active role of this molecule in modulating the TME and posing as a target for intervention. Knowledge on how AFP interacts and coordinate with the TME components would help in creating new approaches to enhance the diagnosis and management of HCC. Further studies should be aimed at a better understanding of the molecular basis of AFP signalling in relation to HCC and the TME and to bring new findings immediately into the clinic for improving patient care for this incurable disease.

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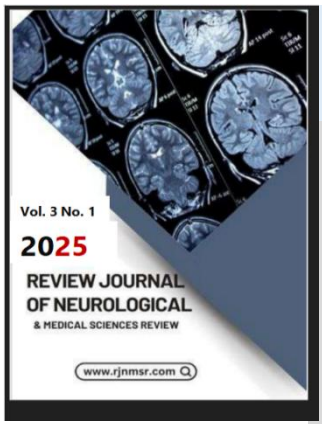

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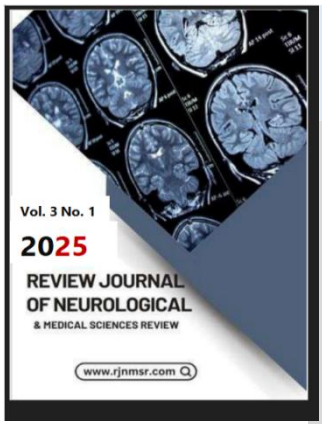

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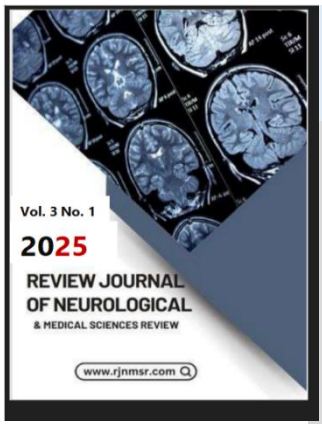

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