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REVIEW ARTICLE

Autophagy Regulators p62/SQSTM1 and NBR1 as new Predictive Biomarkers of Immunotherapy Response in Hepatocellular Carcinoma

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ABSTRACT
Hepatocellular carcinoma (HCC), among the top causes of cancer-associated mortality globally, lacks effective treatment, especially at an advanced stage. While immunotherapy has great promise as an antitumour treatment method, there exist no robust biomarkers for patient response as yet. To evaluate p62 and NBR1 as predictive biomarkers for immunotherapy response. A new biomarker has recently been identified that may be used to predict the efficacy of HCC immunotherapy. Approximately ten articles from Google Scholar and EBSCOhost, selected through a search based on recent mechanistic and preclinical studies, were used for this research. The p62 biomarker enhances STING activation in hepatic stellate cells, and NBR1 (neighbour of BRCA1 gene 1) is an additional key autophagy receptor that plays a comparable role to p62 in sequestering protein aggregates. Early studies suggest that its expression or activation may be used to identify patients who are likely to benefit the most from immune checkpoint inhibitors, thereby producing more effective and personalised treatment approaches. These findings support p62 and NBR1 as promising predictive biomarkers of HCC pending clinical validation.

INTRODUCTION
Hepatocellular carcinoma (HCC) is the most common type of liver cancer, accounting for more than 690,000 new cases globally each year. It is the third most frequent cause of cancer-related death and the fifth most common cancer globally (Sung et al., 2021). Cirrhosis, hepatitis B (HBV), hepatitis C (HCV), and nonalcoholic fatty liver disease (NAFLD) lead to eighty to ninety per cent of HCC cases (Heimbach et al., 2018).

Its male-to-female ratio is 3:1; that is to say, men are more likely to have the condition (Sung et al., 2021). The significant risk factors are likely to include hepatitis B virus and hepatitis C virus (HBV and HCV), cirrhosis of the liver, alcohol consumed in high quantities, metabolic disorders and exposure to aflatoxin. Nonalcoholic fatty Liver Disease, or fatty liver, stems from excess fat accumulation (obesity) and metabolic dysfunction. It is a worsening problem as it progresses to nonalcoholic steatohepatitis (NASH) and cirrhosis; the two aforementioned have a higher risk of aggravating and causing hepatocellular carcinoma (Younossi et al., 2023). Mutations in genes related to liver function and diabetes mellitus also increase susceptibility to the development of HCC (El-Serag et al., 2023).

The stage of cancer and the patient's overall liver functioning could influence hepatocellular carcinoma therapy. Surgical therapies include liver excision for those with good liver function and liver transplantation for those with cirrhosis (Heimbach et al., 2018). Direct tumour destruction is achieved using locoregional therapies such as radiofrequency ablation (RFA), microwave ablation, and cryoablation (Bruix et al., 2019). Transarterial chemoembolisation (TACE) and transarterial radioembolisation (TARE) are used for intermediate-stage HCC through the combination of chemotherapy and embolisation to occlude the vascular supply to the tumour.

Systemic treatment for advanced HCC includes targeted medicines such as sorafenib and lenvatinib, which are used as alternatives to limit tumour growth, along with angiogenesis inhibition (Llovet et al., 2018). Immunotherapy, specifically immune checkpoint inhibitors (e.g., nivolumab and pembrolizumab), has demonstrated efficacy in treating advanced HCC.

Current biomarkers such as AFP and PD-L1 suffer from poor sensitivity/specificity, especially in non-viral HCC. This study investigates p62 and NBR1, which may provide better predictive value by modulating the STING pathway

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and autophagy regulation. Hence, the review is aimed at extracting and analysing information on autophagy regulators p62/SQSTM1 and NBR1 as new predictive biomarkers of immunotherapy response in hepatocellular carcinoma."

METHODS

Data were obtained and retrieved from Google Scholar and EBSCOhost using specific keywords such as 'Autophagy Regulators p62/SQSTM1', 'NBR1 as New Predictive Biomarkers Immunotherapy Response', and 'Hepatocellular Carcinoma'.

Inclusion Criteria: Studies that involved original research articles, reviews, preclinical (in vitro/in vivo) and clinical studies, articles published in peer-reviewed journals and published in English. The search was streamlined to articles published within the last 10 years (e.g., 2014–2024). The study focuses on investigating the role of p62/SQSTM1 and/or NBR1 as biomarkers. Articles discussing proteins in regard to autophagy, cancer biology, or immune regulation. The disease focus was specifically to address Hepatocellular Carcinoma (HCC). In the context of immunotherapy, articles that evaluate or discuss the response to immunotherapy (e.g., immune checkpoint inhibitors, adoptive T-cell therapy) in HCC. Studies linking p62/NBR1 with immunomodulatory mechanisms. Studies providing molecular, cellular, or physiological mechanisms involving p62/NBR1 in autophagy or immune signalling relevant to HCC. Studies using functional assays, such as knockdown/overexpression, autophagy flux analysis, and immune cell profiling, support a predictive or regulatory role. Studies with translational potential, especially those involving human samples or clinical cohorts, were given special preference.

Exclusion criteria: The following were excluded from the review: articles not involving hepatocellular carcinoma and studies that investigate p62/NBR1 in HCC but do not address immune-related outcomes. Studies on p62/NBR1 unrelated to autophagy, tumour immunity, or biomarker research, Studies involving general narrative reviews without novel data or detailed analysis and lastly, articles not written in English.

Immunotherapy and Its Role in HCC

The primary goal of immunotherapy is to harness the body's immune system to target and eliminate cancer cells. Checkpoint inhibitors, such as nivolumab and pembrolizumab, have shown promise in advanced HCC, particularly for patients who have not responded to traditional treatments (El-Khoueiry et al., 2017; Zhu et al., 2018). Tyrosine kinase inhibitor is thought to be less effective than Immunotherapy (Zhu et al., 2018).

However, some patients don't respond to immunotherapy, which underscores the necessity of dependable biomarkers to predict treatment outcomes and inform medical decisions (Piñero et al., 2019). Despite the existence of certain biomarkers, they primarily indicate a bad prognosis, highlighting the need for additional markers that can enhance patient classification, early diagnosis, and treatment efficacy monitoring (Cho et al., 2019; Ren et al., 2019).

The advancement of hepatocellular carcinoma is often associated with chronic inflammation and the progression of an immunosuppressive microenvironment. Cirrhosis and chronic viral infection trigger the production of cytokines that are inhibitory in nature (e.g., IL-10, TGF-β) and cells of immunosuppressive origin (e.g., regulatory T cells, M2 macrophages, and myeloid-derived suppressor cells), which encourage immune lenience and also hinder effective immune responses against tumour cells (Zongyi et al., 2020).

The Need for Biomarkers in Immunotherapy

The treatment of hepatocellular carcinoma has been revolutionised with immunotherapy, although its effectiveness remains unreliable across patients. The advancement of reliable biomarkers to predict response to immunotherapy is necessary for enhancing treatment routine and improving patient survival rates (Ren et al., 2019; Piñero et al., 2019). Noting biomarkers that can help predict early diagnosis, monitor treatment responses, and stratify patients based on their chances of benefiting from immunotherapy will be crucial for improving personalised treatment in HCC (Cho et al., 2019).

Despite advancements in hepatocellular therapy, challenges persist in predicting patient responses and enhancing treatment outcomes. Identifying novel biomarkers will be key to enhancing patient outcomes and ensuring more effective, personalised treatments.

Mechanism of Immunotherapy in Hepatocellular Carcinoma (HCC)

Immunotherapy for hepatocellular carcinoma (HCC) influences both passive and active strategies to modulate the immune system and counteract tumour advancement.

Passive-Mediated Immunotherapy: This method primarily involves the use of immune checkpoint inhibitors (ICIs) and tumour vaccines, in addition to adoptive cell therapies, to either block or counteract the immunosuppressive tumour environment characteristic of hepatocellular carcinoma. The aforementioned therapies target various immune evasion devices employed by the tumour. For example, certain strategies focus on deactivating inhibitory cytokines or obstructing their production to re-establish immune functioning (Yang et al., 2019). Active Immunotherapy: This mechanism tries to restore the natural cancer-immunity cycle, which is necessary for eradicating tumour cells. The cycle reveals itself in several key steps: Antigen Capture and Processing: Tumour-derived antigens are primarily captured and processed by dendritic cells (DCs), which are essential in presenting immune responses. T-Cell Activation: These processed antigens are then presented to T cells, exciting them to identify and respond to cancer-specific antigens (Chen and Mellman, 2013). Tumour Cell Elimination: Later activation, T cells penetrate the tumour microenvironment, where they specifically target and

eliminate tumour cells that express the identified antigens (Chen and Mellman, 2013).

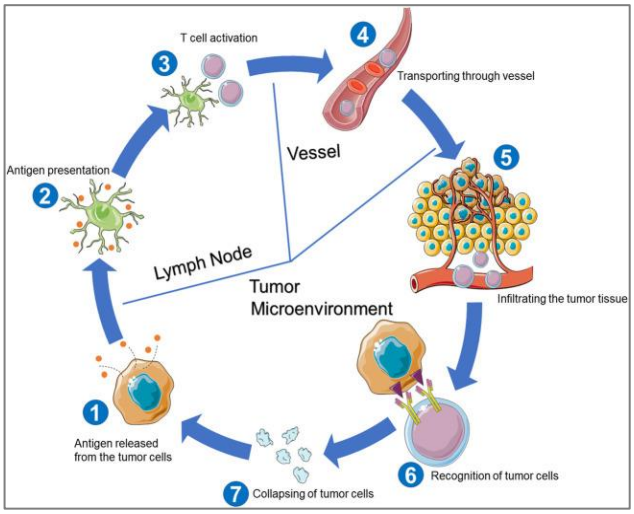

Fig 1.1 Cancer-immunity cycle for killing tumor cells (Chen and Mellman, 2013).

2.4 Current immunotherapies for HCC

The current immunotherapies for HCC are: Alpha-fetoprotein (AFP), CAR-T: Chimeric antigen receptors engineered T cell (CAR-T), CTLA4: Cytotoxic T lymphocyte antigen (CTLA4), Interferon-alpha (IFN): Interleukin-2 (IL-2): Natural killer (NK): Programmed cell death-1 (PD-1): and Programmed cell death-ligand 1 (PD-L1) (Zongyi and Xiaowu,2020 and Sangro *et al.*, 2021).

Biomarkers in HCC

A diagnostic biomarker can be defined as any substance, structure, or method that can be detected and quantified in the body to indicate the presence, progression, or response to treatment of a disease (Ferrín et al., 2015). For hepatocellular carcinoma, a perfect biomarker should possess several key qualities for routine medical use: it should be sensitive, specific, inexpensive, easy to measure, highly reproducible, and capable of providing rapid results.

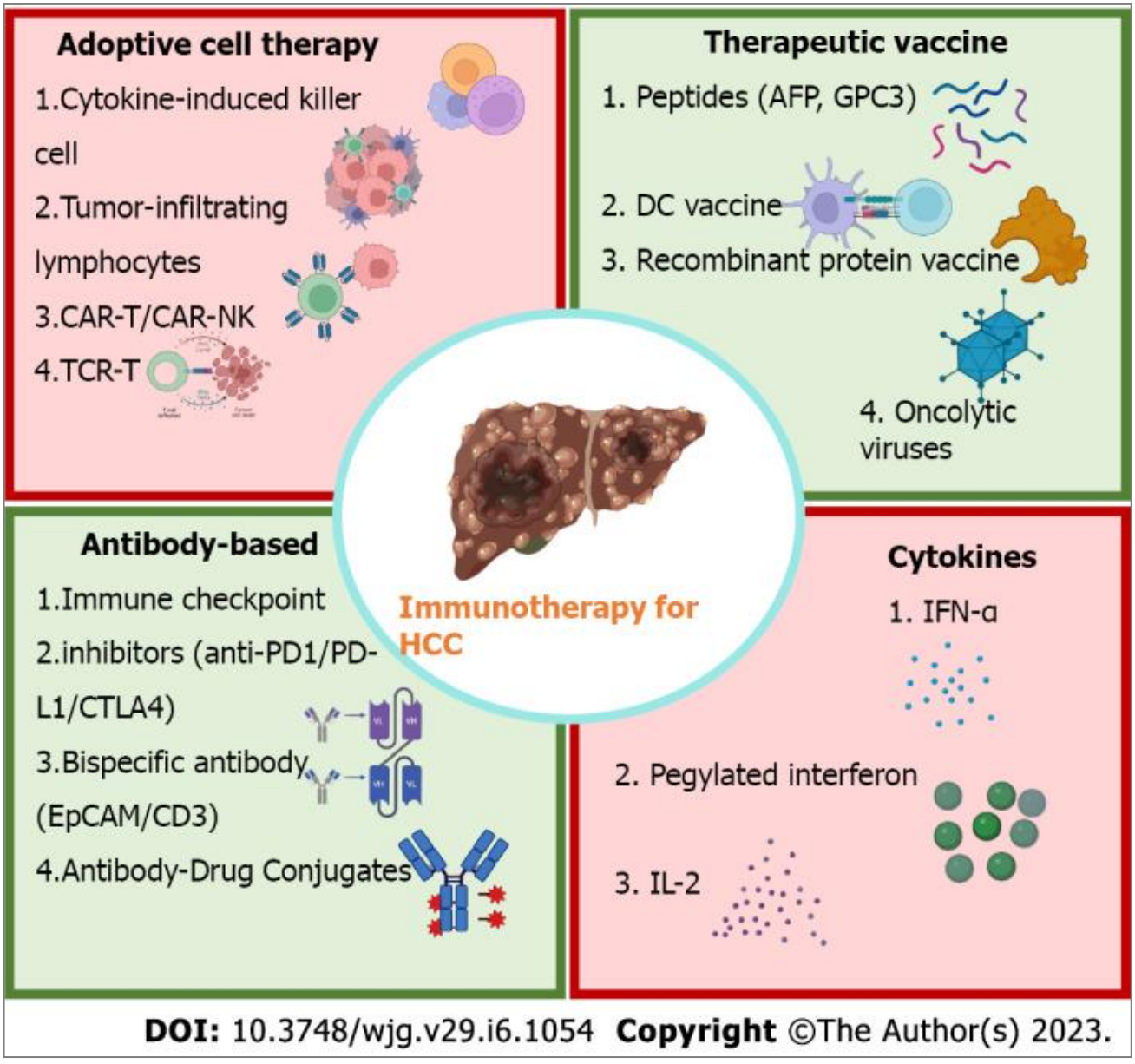

Fig 1.2 Recent immunotherapies for HCC (Ducreux *et al.*, 2023)

Furthermore, it should correlate with tumour growth progression and, if possible, be detectable in easier, more accessible samples, such as blood or urine, without the need for therapy (Ferrín et al., 2015). Hepatocellular carcinoma biomarkers can be considered based on their biochemical properties, and the method of identification remains crucial in improving early diagnosis, monitoring disease progression, and assessing treatment potential (Ferrín et al., 2015).

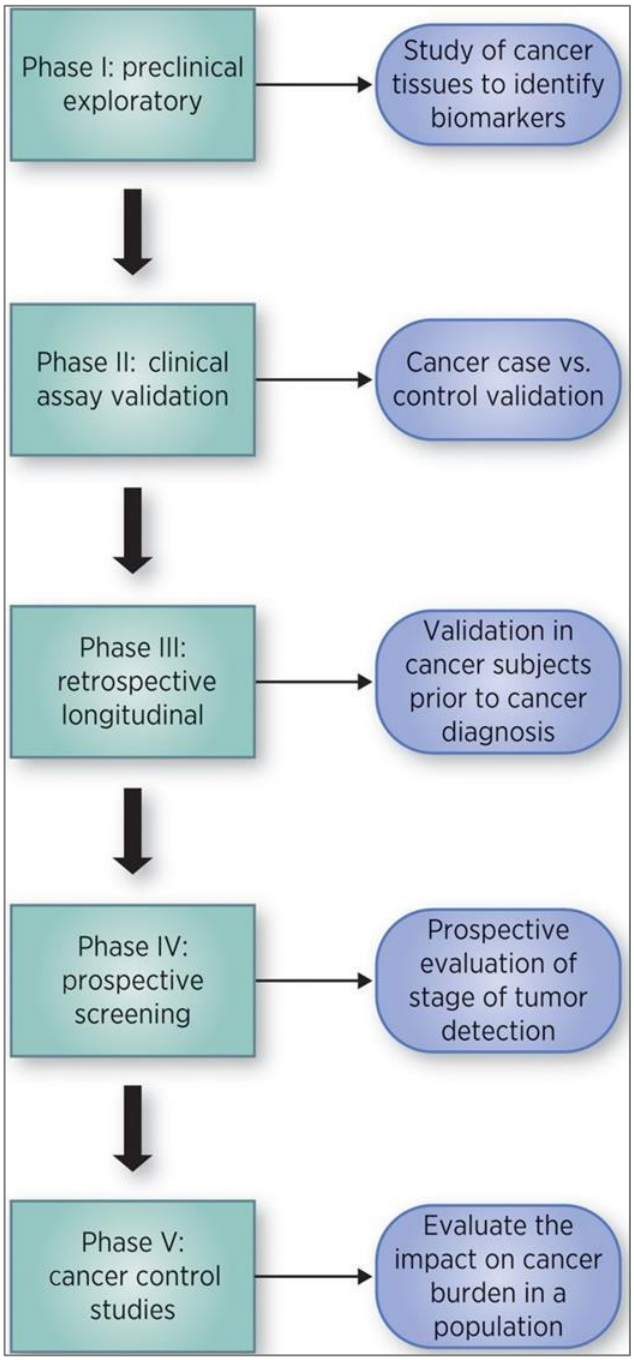

Fig 1.3 : Phases of Clinical Biomarker validation (Tzartzava *et al.*, 2018).

Current Challenges in HCC Treatment

Current studies have shown that immune checkpoint inhibitors (ICIs) are less effective in patients with non-virally induced hepatocellular carcinoma (HCC). Non-viral origins of hepatocellular carcinoma include conditions such as obesity and diabetes, nonalcoholic steatohepatitis (NASH), as well as environmental and lifestyle factors such as excess alcohol consumption, unguided tobacco use, contact with aflatoxins, iron overload syndromes, and the unregulated use of oral contraceptives or betel quid chewing (Pfister et al., 2021). Furthermore, the prognosis for hepatic cancer remains poor, with inadequate therapeutic choices available (El-Serag et al., 2019). A noteworthy number of patients also advance in resistance to treatments like transarterial chemoembolisation (TACE) and the kinase inhibitor sorafenib within six months of initiation, often with adverse drug reactions and toxicity, especially from continued use (El-Serag et al., 2021).

2.7 Existing Biomarkers for Immunotherapy Response

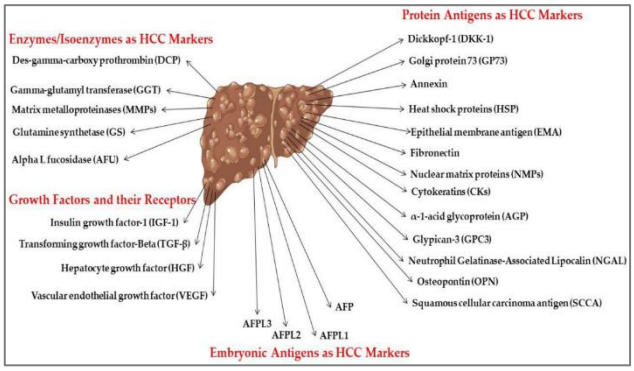

Fig 1.4: HCC marker classification according to biochemical nature (Wang and Wei, 2020).

Limitations of Current Biomarkers

Alpha-fetoprotein (AFP) has been the most widely accepted biomarker for the diagnosis and surveillance of hepatocellular carcinoma (HCC) for a long time, and it has reached phase 5 in the biomarker development phases. However, the efficacy of alpha-fetoprotein (AFP) is limited by several notable shortcomings. For example, when a higher cutoff value, such as 200 ng/mL, is utilised in improving specificity, its sensitivity drops considerably to only 22% (Gonzalez, 2014; Schütte et al., 2015). As a result of the aforementioned, the use of alpha-fetoprotein in clinical practice is hindered by the trade-off between maintaining a high level of specificity and the relatively low sensitivity at these cutoff levels. Although alpha-fetoprotein is considered a prognostic marker, it is less effective in guiding treatment decisions, particularly in patients with normal AFP levels before treatment (Zhu et al., 2018). Another challenging aspect of alpha-fetoprotein is the lack of consensus on when post-treatment AFP levels should be measured, which contributes to the uncertainty in its clinical application (Zhu et al., 2018). Moreover, the role of alpha-fetoprotein in assessing treatment response, especially in patients undergoing sorafenib therapy, has yet to be validated in prospective studies (Zhu et al., 2018).

While alpha-fetoprotein remains the primary biomarker for early detection, prognosis, and monitoring response to treatment in hepatocellular carcinoma, its limitations—predominantly in terms of sensitivity and specificity—are considerable, especially when utilised in isolation.

Sensitivity can vary from 20% to 60%, and specificity can vary from 80% to 100% (Wang and Wei, 2020). These restrictions underscore the pressing need for additional or complementary biomarkers to enhance the clinical management and care of hepatocellular carcinoma patients (Chen et al., 2020; Heimbach et al., 2018).

PD-1 and PD-L1

Immune checkpoint inhibitors (ICIs), which target immune barriers like Programmed Cell Death-1 (PD-1) and Programmed Cell Death Ligand-1 (PD-L1), purpose to excite the immune system to selectively eradicate cancer cells (Vogel and Saborowski, 2020). Notwithstanding the promise of immune checkpoint inhibitors, the objective response degree in hepatocellular carcinoma remains comparatively low, stereotypically around 30% (Finn et al., 2020).

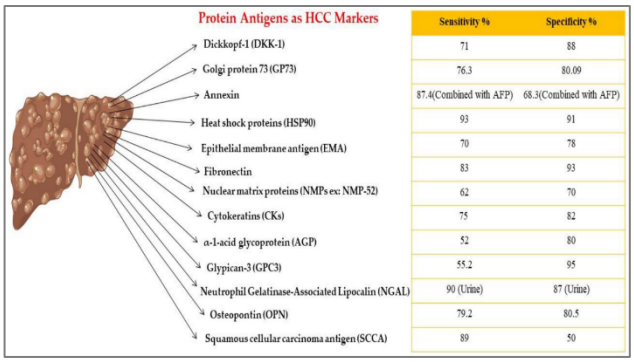

Fig 1.5: Sensitivity and Specificity of some Protein Antigen biomarkers (Wang and Wei, 2020).

The New Biomarkers for HCC

gp62 / SQSTM1 (Sequestosome 1)

SQSTM1, or Sequestosome 1, is a gene that encodes the p62 protein, which spans approximately 16 kb on chromosome 5 (Sanchez-Martin et al., P62 functions as a multi-functional signalling hub and autophagy adaptor, promoting both the process of autophagy and the degradation of ubiquitinated proteins (Sanchez-Martin et al., 2019). Autophagy is a crucial cellular reutilization mechanism that involves the engulfment of substrates in double-membraned vesicles called autophagosomes (Sanchez-Martin et al., 2019). In several cancers, as well as hepatocellular carcinoma (HCC), raised levels of p62 are frequently observed in tumour cells (Sanchez-Martin et al., 2019). In these cells, improved p62 expression triggers key signalling pathways such as Nrf2 (nuclear factor erythroid 2-related factor 2), mTORC1 (mechanistic target of rapamycin complex 1), and NF-ϰB (nuclear factor-kappa B), all of which contribute to cancer cell progress and proliferation (Shimizu et al., 2016). Additionally, increased levels of p62-positive inclusion bodies, known as Mallory–Denk bodies, are frequently initiated in individuals with chronic hepatic diseases, including hepatocellular, nonalcoholic steatohepatitis (NASH), alcoholic hepatic disease, and other metabolic disorders (Sanchez-Martin et al., 2018). As a result, p62 expression has emerged as a promising diagnostic and prognostic marker for hepatocellular carcinoma, potentially offering a benefit over biomarkers like PD-1 and PD-L1, which have limited effectiveness in non-virally associated hepatocellular carcinoma (Pfister et al., 2021).

NBR1

NBR1 (neighbour of BRCA1 gene 1) is an additional key autophagy receptor that plays a comparable role to p62 in sequestering protein aggregates. It works together with p62 to help facilitate this process; nonetheless, it also has a unique capacity to bind to monoubiquitin, unlike p62, which principally interacts with polyubiquitinated proteins (Kelsey et al., 2022). This characteristic function of NBR1 suggests its potential as a complementary biomarker together with p62, further refining our thoughtfulness of the autophagy and immune pathways involved in hepatocellular carcinoma progression.

Mechanism of Action:

By promoting the activation of the interferon (IFN) cascade in hepatic stellate cells, p62 enables the ubiquitination of STING stimulator of interferon genes (STING) by the tripartite motif protein 32 (TRIM32) (Saadaki et al., 2024). P62 interrelates with NBR1 and the stimulator of interferon genes, triggering the IFN cascade by displacing NBR1, which normally hinders the interaction between TRIM32 and the stimulator of interferon genes, thereby preventing STING activation. On the other hand, NBR1 antagonises the stimulator of interferon genes by promoting its trafficking to the endosomal-lysosomal compartment for degradation, thereby facilitating self-determination of autophagy (Saadaki et al., 2024).

Preclinical Studies Supporting P62 and NBR1 as Predictive Biomarkers

Fibrosis, which resulted from chronic hepatic injury, is categorised by the deposition of extracellular matrix (ECM) proteins, predominantly collagens, by activated hepatic stellate cells (Kisseleva and Brenner, 2021). Excessive activation of hepatic stellate cells exacerbates fibrosis and promotes the progression of hepatocellular carcinoma by secreting pro-inflammatory cytokines (Duran et al., 2016).

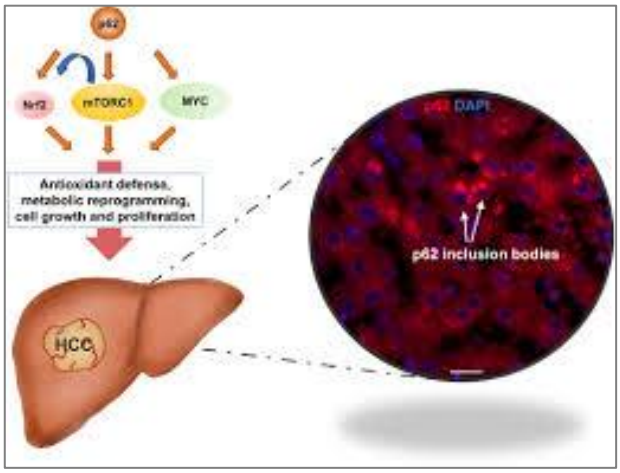

Fig. 1.6: Antioxidant Defence Metabolic Reprogram (Duran et al., 2016)

In human hepatocellular carcinoma, p62 expression is increased in hepatocytes but downregulated in hepatic stellate cells (Duran et al., 2016). Interestingly, the buildup of p62-positive inclusion bodies in hepatic cells is progressively recognised as a biomarker for NASH and hepatocellular carcinoma, with their levels agreeing with disease development and prognosis (Chong et al., 2021). Preclinical studies in mouse models have also shown that p62 potentiates the activation of hepatic stellate cells, driving liver fibrosis and inflammation, which hastens hepatocellular progression in models involving diethylnitrosamine (DEN) and a high-fat diet (Duran et al., 2016).

The interaction amid p62 (also known as SQSTM1) and the neighbour of the BRCA1 gene 1 (NBR1) in HCC critically influences the tumour microenvironment and immune response. Recent findings shown in silico analyses have elucidated their antagonistic roles, principally regarding the STING (stimulator of interferon genes) pathway in hepatic stellate cells (HSCs). Mendeley Data, 2024.

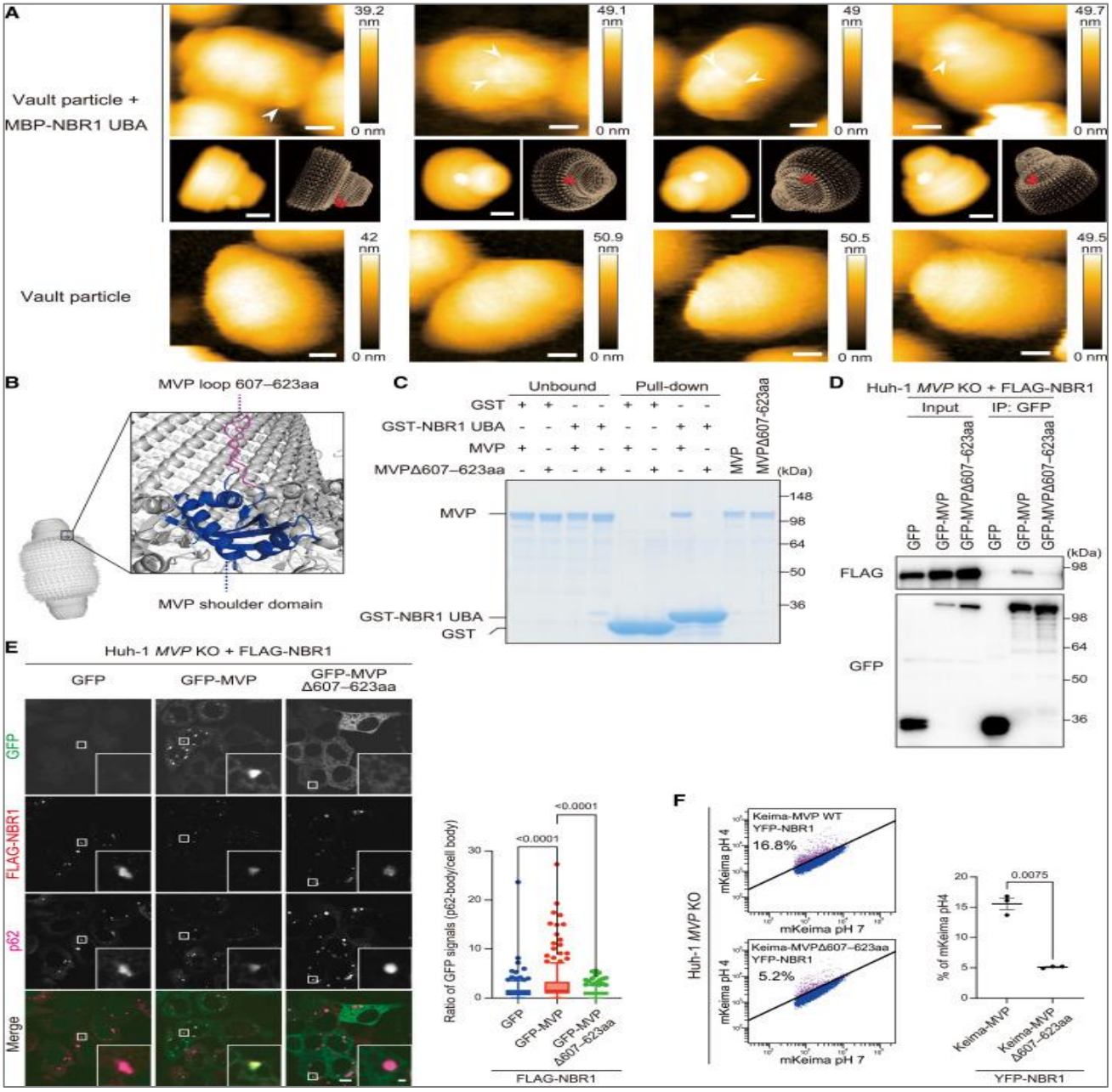

Fig. 1.7: Interaction Between p67, BRCA1 in HCC (Mendeley Data, 2024; Nishimura et al., 2024)

Antagonistic Roles of p62 and NBR1 in HCC

In hepatic stellate cells, p62 helps facilitate the stimulation of the STING pathway by helping the ubiquitination of STING via the E3 ligase TRIM32. These aforementioned processes help enhance the interferon (IFN) cascade, contributing to an inflammatory microenvironment that provides the necessary support for tumour progression. In addition, NBR1 acts as a negative regulator of STING by sequestering it in the endosomal-lysosomal compartment, leading to its degradation independently of autophagy. This degradation damages the IFN response, thus overwhelming antitumour immunity.

The balance between p62 and NBR1 determines the activation state of the STING pathway, as demonstrated

by a computational model. In situations where p62 is low, the presence of NBR1 can restore STING activation, thereby enhancing the IFN response and promoting antitumor CD8+ T cell activity (Mendeley Data, 2024; Nishimura et al., 2024). This suggests that NBR1 loss in p62-deficient HSCs can revert the tumour-promoting phenotype, stressing NBR1 as a potential therapeutic target in hepatocellular carcinoma.

In Silico Modelling and Data Integration

The interaction between p62, NBR1, and STING was modelled in this study using these data. Understanding the changes in gene expression modulation of these three proteins in HSCs was made easier by these data, which were published on Omics DI. The effects of p62 and NBR1 on STING and immune response in HCC were then determined by integrating this data into computational models that simulated every potential pattern (Nishimura et al., 2024).

NBR1 and p62 antagonising roles in silico models have proven invaluable in dissecting these connections, offering likely paths for beneficial interference targeting the p62-NBR1 axis to help enhance antitumour immunity in Hepatocellular Carcinoma (Omics, 2024).

Table 1: Biomarker Expression Levels

Biomarker	Expression Level	% of Patients
p62	+	48%
p62	–	52%
LC3	+	60%
LC3	–	40%
Beclin-1	+	55%
Beclin-1	–	45%
p53	+	65%
p53	–	35%

This table shows the proportion of patients with a specific biomarker (e.g., p62) present at either a high ("+") or absent ("-") level.

Table 2: Immunotherapy Response Stratified by Biomarker (Chen et al., 2021)

Biomarker Status	Immunotherapy Response Rate (%)
$p62^{+}$	45%
$p62^{-}$	22%
PD-L1 High	58%
PD-L1 Low	18%

This table compares the response rates to an immunotherapy treatment (e.g., checkpoint inhibitors) for different patient groups based on their biomarker expression levels.

DISCUSSION

NBR1 and p62 (also referred to as SQSTM1) are receptors for selective autophagy, functioning as cargo adaptors crucial for the autophagic degradation of ubiquitinated proteins. Their mechanistic uniqueness stems from their dual roles in protein degradation and cell signalling, such as in the Keap1–Nrf2 pathway, a signalling pathway for oxidative stress (Komatsu & Ichimura, 2010). In cells lacking autophagy, p62 will accumulate and form inclusion bodies that are visible in many diseases, including HCC, certain neurodegenerative disease conditions, and inflammatory conditions.

In addition, NBR1 also associates with p62 to participate in selective removal of damaged organelles and protein aggregates, while p62, by cross-talk signalling including UBA, PB1, and LIR, enables interaction with other autophagy routes (Kirkin et al., 2009). Therefore, p62 and NBR1 together are dynamic markers for depicting defective autophagic processes within a cell, which reflect cellular malfunction and stress, rather than being tumour static markers.

Unconventional traditional biomarkers, such as alpha-fetoprotein (AFP) in liver cancer or PD-L1 in immunotherapy, as well as p62/NBR1, help provide a necessary real-time snapshot of cell stress and autophagy. Each of AFP and PD-L1 comes with its own limitations. For example, AFP is unspecific and rises only in the later stages of hepatocellular carcinoma (HCC). PD-L1 expression is also heterogeneous, varying with treatment, and generally asymmetrically distributed (Cheng et al., 2020; Patel & Kurzrock, 2015). In contrast, p62/NBR1 can detect proteostatic alterations much earlier on long before clinical disease or evidence of cancer can be detected. In relation to PD-L1, which has been mostly utilised to forecast immunotherapy responses, p62/NBR1 likely has a broader array of diagnostic and prognostic applications in diseases where autophagy is defective. They are metabolic disorders, cancer, and neurodegenerative diseases.

There are significant disadvantages in using p62/NBR1 as biomarkers in the clinic, despite possible prospects. There is no universally accepted standard measurement method. Detection methods, such as western blotting and immunohistochemistry, do not have standardised procedures or protocols across laboratories. Context dependence and tissue specificity: Expression levels are tissue-dependent, disease-stage-dependent, and influenced by other diseases or conditions. The duality of cancer: The two opposing roles of p62, as either cancer-causing or cancer-preventing, depending on the context (Moscat & Diaz-Meco, 2012), render its interpretation complex. Disease-modifying therapies' influence: Chemotherapy, radiation, and even immunotherapy may modulate autophagy, which may alter p62/NBR1 levels regardless of disease progression.

RECOMMENDATIONS

This would require large, multicenter studies to confirm the projecting capability of p62 and NBR1 in various

patient populations, ensuring the usefulness of the biomarker is applicable across the board. Biomarker testing for p62 and NBR1 would then need to be incorporated into standard clinical practice for hepatocellular carcinoma, with an established guidelines regimen to assist health professionals in interpreting results and making evidence-based treatment decisions. These experts must be reflective as well as knowledgeable regarding the effects of these biomarkers on treatment, safeguarding the effective utilisation of this novel information in the treatment of patients.

CONCLUSION

A noteworthy step toward cancer therapeutics and treatment regimes begins by identifying p62 and NBR1 as predictive biomarkers for immunotherapy response in hepatocellular carcinoma treatments. The two biomarkers p62 and NBR1 regulate STING-mediated IFN response in hepatic stellate cells. Their biomarker potential in HCC immunotherapy requires clinical validation and integration into practice."

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