Research Abstract 03:

Sirtuin-1 in Hepatocellular Carcinoma: Roles in Hypoxia, Stress Adaptation and Therapeutic Potential

Nur Diyana Zulkifli[1], Nurulisa Zukifle[1,2]

[1]Department of Biomedical Science, Advanced Medical and Dental Institute, Universiti Sains Malaysia, Sains@Bertam, 13200 Kepala Batas, Pulau Pinang, Malaysia.
[2]Advanced Management of Liver Malignancies (Liver-ENRICH) Research Program, Advanced Medical and Dental Institute, Universiti Sains Malaysia, 13200 Kepala Batas, Pulau Pinang, Malaysia.

*Correspondence: nurulisa@usm.my

Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver cancer and ranks among the leading causes of cancer-related deaths worldwide. Despite improvements in surveillance and treatment, prognosis remains poor. One of the major obstacles to effective therapy is the presence of tumour hypoxia. As HCC nodules expand beyond their vascular supply, they develop oxygen-deficient niches that reshape tumour behaviour. Hypoxia promotes angiogenesis, drives metabolic reprogramming and reduces the effectiveness of chemotherapy, radiotherapy and immunotherapy [1]. Hypoxia is particularly severe in the liver because of its dual blood supply and the frequent presence of cirrhotic or fibrotic tissue, which further impairs oxygen delivery.

Hypoxia is not simply oxygen deprivation. It represents a complex cellular stress that impairs mitochondrial respiration, amplifies oxidative damage and activates pathways leading to cell death. Tumour cells that survive in this environment must activate adaptive programmes to maintain energy production and prevent irreversible injury. Sirtuin-1 (SIRT1), an NAD^+-dependent deacetylase, is a central regulator of such adaptations. Early mechanistic work demonstrated that SIRT1 modulates transcriptional regulators including p53, FOXO proteins, PGC-1α and NF-κB, providing an important link between nutrient and oxygen sensing, stress response and survival [2-5].

SIRT1 as a Regulator of Stress Adaptation

SIRT1 contributes to survival through several interconnected mechanisms rather than isolated pathways. By deacetylating p53 it reduces pro-apoptotic transcription, while modification of FOXO transcription factors favours antioxidant and repair pathways [2,3]. Activation of PGC-1α stimulates mitochondrial biogenesis and supports energy production in conditions of nutrient or oxygen limitation [4]. Modulation of NF-κB activity reduces inflammatory signalling, further contributing to tissue protection [5]. Collectively, these mechanisms establish a chain of protective responses in which SIRT1 coordinates apoptosis suppression, antioxidant defence, mitochondrial renewal and inflammation control.

More recent studies expand these classical roles. SIRT1 regulates autophagy via AMPK and mTOR signalling, enabling cells to recycle components and preserve ATP supply during stress [6]. It also participates in immune-metabolic regulation by influencing macrophage polarisation and cytokine production, thereby shaping the tumour microenvironment [7]. In addition, SIRT1 has been linked to senescence regulation and epigenetic stability, connecting redox balance to long-term cell survival and chromatin integrity [8]. Together these activities highlight SIRT1 as a network integrator that coordinates multiple arms of the stress response.

SIRT1 in Hepatocellular Carcinoma and Hypoxia

Clinical observations show that SIRT1 is often overexpressed in HCC compared with adjacent normal liver tissue. Elevated expression correlates with larger tumour size, vascular invasion, poor differentiation and unfavourable prognosis [9]. Transcriptomic analyses at single-cell resolution further reveal that hypoxia-adapted tumour clusters display strong SIRT1 activity, consistent with roles in glycolytic metabolism, angiogenesis and stress tolerance [10].

Functional studies illustrate the heterogeneity of SIRT1 responses under hypoxia. In some settings, SIRT1 deacetylates and stabilises hypoxia-inducible factor-1α (HIF-1 α), supporting glycolysis and

vascular growth. In others, SIRT1 levels decrease during prolonged hypoxia, shifting its role toward genome stability and restraint [11]. These contrasting outcomes reflect differences in tumour genotype, mitochondrial capacity and microenvironmental state. A consistent theme, however, is that SIRT1 provides flexibility that allows cells to adapt to hypoxic stress, which in turn influences tumour progression and therapy resistance.

Therapeutic Potentials

Given its central role in adaptation, SIRT1 is an attractive therapeutic target. Pharmacological strategies have pursued both activation and inhibition. Activators such as resveratrol and synthetic analogues aim to enhance mitochondrial function and antioxidant defence, whereas inhibitors are designed to block survival pathways in tumours. The selective inhibitor EX-527 has entered clinical testing for safety and in recent preclinical studies has enhanced the activity of cytotoxic agents, including paclitaxel, in resistant cancer models [12]. However, translation to the clinic has been challenging because the outcome of SIRT1 modulation is strongly context dependent. Tumour heterogeneity, compensatory signalling networks and the dual nature of SIRT1 as both protector and enabler mean that interventions may succeed in one biological state and fail in another. This underlines the need for biomarker-driven approaches that define when to inhibit and when to activate SIRT1 in HCC.

Advances in genome engineering have created new tools for exploring SIRT1 biology. CRISPR/dCas9-based transcriptional regulators allow targeted activation or repression of the endogenous SIRT1 promoter without altering the genome permanently. These models provide more physiologically relevant systems than transient overexpression or knockdown and could been applied to investigate how SIRT1 influences hypoxia tolerance, drug resistance and stress adaptation [13]. When combined with single-cell and spatial profiling, they enable the mapping of SIRT1-dependent niches within tumours and may guide biomarker-driven therapeutic strategies.

Future Perspectives

Translating SIRT1 modulation into therapy requires context-aware approaches. Inhibition is most promising in tumours with high hypoxia signatures and elevated autophagy, where disrupting stress buffering could expose metabolic vulnerabilities and increase sensitivity to chemotherapy. Activation strategies may be relevant in tumours with low mitochondrial reserve and limited autophagic capacity, where enhancing metabolic resilience might sensitise cells to treatment. A rational path forward is to integrate molecular profiling with pharmacological modulation to identify which tumour states are likely to respond to each approach.

Priorities for future research include the development of biomarker panels that incorporate hypoxia scores, autophagy activity and mitochondrial function, systematic testing of SIRT1 modulators in stratified models and early-phase clinical trials that incorporate spatial profiling of hypoxia and sirtuin activity. Such strategies will determine whether SIRT1 can move from a controversial molecular factor to a clinically actionable target in hepatocellular carcinoma.

Conclusion

SIRT1 is positioned at the crossroads of hypoxia adaptation, metabolic control and immune regulation in hepatocellular carcinoma. Foundational studies linked it to apoptosis and mitochondrial function, while recent work has highlighted broader roles in autophagy, immune-metabolic signalling and senescence. The apparent duality of SIRT1 reflects its state-dependent functions. By combining modern genetic tools, advanced profiling technologies and biomarker-guided pharmacological strategies, it may be possible to harness SIRT1 as a therapeutic lever and improve outcomes in hepatocellular carcinoma.

Keywords: *SIRT1; hepatocellular carcinoma; hypoxia; stress response; therapeutic target*

References:

1. Semenza GL. Hypoxia-inducible factors in physiology and medicine. Cell. 2012;148:399-408.
2. Vaziri H, et al. hSIR2(SIRT1) functions as an NAD-dependent p53 deacetylase. Cell. 2001;107:149-59.
3. Brunet A, et al. Stress-dependent regulation of FOXO transcription factors by the SIRT1 deacetylase. Science. 2004;303:2011-15.

4. Nemoto S, Fergusson MM, Finkel T. SIRT1 functionally interacts with the metabolic regulator and transcriptional coactivator PGC-1α. J Biol Chem. 2005;280:16456-60.
5. Yeung F, et al. Modulation of NF-kappaB-dependent transcription and cell survival by the SIRT1 deacetylase. EMBO J. 2004;23:2369-80.
6. Tang Y, et al. The role of SIRT1 in autophagy and drug resistance. Front Pharmacol. 2024;15:1469830.
7. Son Y, et al. SIRT1-mediated redox and senescence regulation in cancer: Mechanisms and therapeutics implications. Antioxidants. 2025;14(9):1076.
8. Zhang Y, et al. Involvement of SIRT1-mediated aging in liver diseases. Front Cell Dev Biol. 2025;13:1548015.
9. Ceballos MP, Quiroga AD, Palma NF. Role of sirtuins in hepatocellular carcinoma progression and multidrug resistance: Mechanistical and pharmacological perspectives. Biochem Pharmacol. 2023;212:115573.
10. Liang J, Chen D, Liang H. Deciphering hypoxia's role in hepatocellular carcinoma prognosis with single-cell approaches. Discov Oncol. 2025;16(1):1411.
11. Cao P, et al. Sirtuin1 attenuates acute liver failure by reducing reactive oxygen species via hypoxia inducible factor 1α. World J Gastroenterol. 2022;28(17):1798-1813.
12. Broussy S, Laaroussi H, Vidal M. Biochemical mechanism and biological effects of the inhibition of silent information regulator 1 (SIRT1) by EX-527 (SEN0014196 or selisistat). J Enzyme Inhib Med Chem. 2020;35(1):1124-1136.
13. ND Zulkifli, et al. Establishment of CRISPR/Cas9-mediated SIRT1 knockdown and overexpression in HepG2 Cells. Malays J Biochem Mol Bio. 2024;Special Issue:67-76

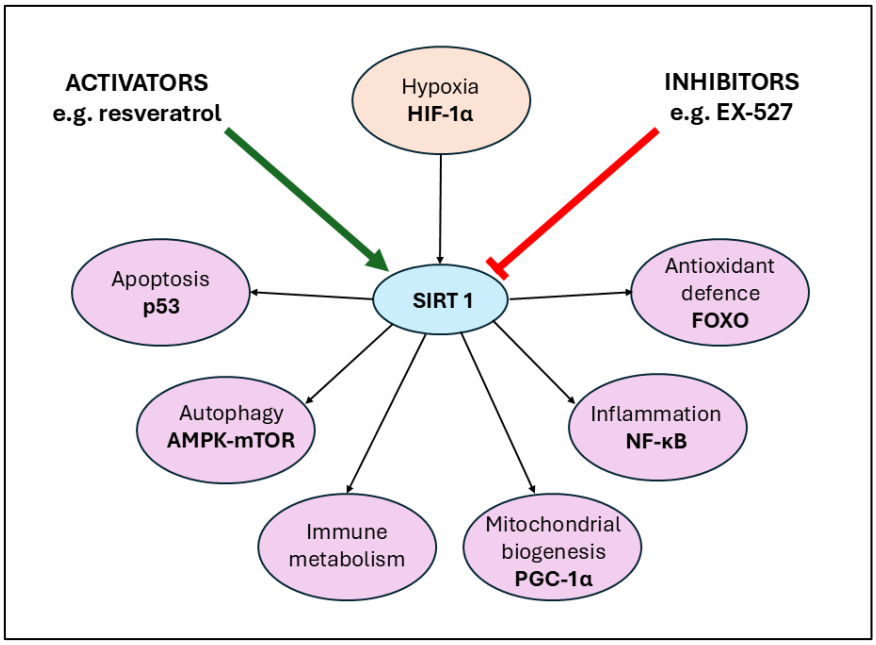

Figure 1. SIRT1 as a central regulator of hypoxia adaptation in HCC: SIRT1 integrates hypoxia signals and pharmacological modulation to control apoptosis, antioxidant defence, mitochondrial biogenesis, inflammation, autophagy, and immune–metabolic pathways, enabling tumour survival and therapy resistance in HCC.