Perspective
Volume 11:03, 2023

Journal of Phylogenetics & Evolutionary Biology

ISSN: 2329-9002 Open Access

Exploring the Impact of Endoplasmic Reticulum Stress on Renal Cell Carcinoma: Navigating an Evolutionary Biology Framework

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Introduction

The endoplasmic reticulum is an organelle that is necessary for protein synthesis, metabolic balance, and cell signalling. The endoplasmic reticulum's ability to perform its regular tasks is compromised when cells are damaged. The so-called unfolded protein response, which is triggered by the activation of specific signalling pathways, has a substantial impact on the fate of cells. Depending on the severity of cell damage, these molecular processes in healthy renal cells either stop or reverse cell injury. As a result, novel therapeutic strategies, such as activating the endoplasmic reticulum stress pathway, have been proposed for diseases like cancer.

On the other hand, it is known that these stress processes are hijacked by renal cancer cells, who then exploit them to their advantage to increase their chances of surviving through metabolic rewiring, activation of oxidative stress responses, autophagy, suppression of apoptosis, and senescence. Recent research clearly implies that cancer cells need to activate their endoplasmic reticulum to a specific degree in order to change their pro-survival endoplasmic reticulum stress responses to pro-apoptotic ones. There are already a number of endoplasmic reticulum stress pharmacological modulators of therapeutic interest, but only a small number have been studied in the context of renal cancer, and it is unknown how they would behave *in vivo* [1].

Description

Renal cell carcinoma is mostly caused by tubular cells, but other types of kidney cells have also been implicated in the development of this cancer. Smoking, obesity, diabetes, hypertension, chronic kidney disease, and exposure to radiation and toxins such as trichloroethylene are all risk factors. Other rare hereditary conditions that can increase the risk of RCC include von Hippel-Lindau syndrome, Birt-Hogg-Dubé syndrome, and Tuberous Sclerosis syndrome. Patients' survival is highly dependent on the stage of the disease at the time of diagnosis. Tumors are staged based on their size and invasiveness, with only 12% of patients with stage tumours surviving 5 years after diagnosis [2].

The kidney performs critical physiological functions in the body, such as blood filtration and pressure regulation, drug metabolism and glycemia control, and toxic metabolite excretion. Tubular cells are the most abundant cell type in the kidney and play an important role in the filtration/reabsorption processes as well as glycemic control. Thus, these cells are highly metabolically active and have high energetic requirements, which are usually met by lipid -oxidation but can also be met by glycolysis in pathological conditions. Tubular cells are particularly vulnerable to stress-induced cell injury associated with drug/metabolite toxicity and ischemic episodes, which can lead to the development of renal cancer with chronicity [3].

As demonstrated in different RCC patient cohort studies, the most commonly used TKI have conflicting results in terms of patient benefit, indicating that the underlying molecular mechanisms involved in RCC are more complex and likely require combined therapies. Nephrectomy is also an option, particularly in advanced cases of RCC. However, only a small number of patients are eligible for these procedures, which are limited by the tumor's location and accessibility, associated comorbidities, and the severity of the symptoms. Finally, radiotherapy can be used in patients with metastatic RCC, but the patients' survival is not improved. As a result, novel therapeutic options are required to optimise RCC treatment.

The type of mutations driving carcinogenesis influences metabolic reprogramming of renal cancer cells. In humans, for example, ccRCC is characterised by aerobic glycolysis and pseudohypoxia, as well as activation of the pentose phosphate pathway and decreased oxidative phosphorylation, which are hallmarks of Warburg-like reprogramming. These metabolic characteristics are consistent with the cancer type's recurrent loss of the tumour suppressor VHL. VHL ubiquitinates and targets for degradation, and its loss cause HIF1 accumulation and activation of hypoxia responsive factors, glycolysis, and glucose uptake in renal tubular cells. VHL mutations are also linked to an increase in the expression of the pro-angiogenic vascular endothelial growth factor and the mammalian target of rapamycin pathway, which is a key regulator of cell proliferation, energy metabolism, and autophagy [4,5].

When cellular damage is deemed irreversible, the ability of the UPR to trigger either pro-survival or pro-apoptotic mechanisms is very appealing for therapeutic purposes in diseases such as cancer and deserves consideration when considering personalised medicine approaches. Several critical factors in ER stress signalling must be better understood before these molecular pathways can be used as therapeutic targets. To begin, it is critical to precisely define the level of cell damage above which ER stress becomes irreversible and activates the pro-apoptotic machinery. This limit, from which the UPR induces a switch from a pro-survival to a pro-apoptotic response, is still unknown and is thought to be highly variable across cell types, tissues, and/or organs.

Conclusion

The determination and standardisation of basal UPR activation levels in patients' tumours is also required in order to move forward with these personalised medicine approaches, whether the goal is to effectively hyperactivate ER stress in RCC or to sensitise RCC to a particular treatment by suppressing ER stress signalling. In addition to the conventional assessments of mRNA expression, XBP1 splicing, or protein assessments of total phosphorylated UPR effectors, new standardised methodologies and quantitative measurements of ER stress in patients' tumours must be created. This calls for the creation of a standardised multi-parametric activation/inhibition range for the UPR, which would unmistakably show the ideal ER stress modulation approach for a specific patient.

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Received: 20 May, 2022, Manuscript No: JPGEB-23-106367; **Editor assigned:** 22 May, 2023, PreQC No: P-106367; **Reviewed:** 05 June, 2023, QC No: Q-106367; **Revised:** 10 June, 2023, Manuscript No: R-106367; **Published:** 17 June, 2023, DOI: 10.37421/2329-9002.2023.11.277

Acknowledgement

None.

Conflict of Interest

There are no conflicts of interest by author.

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How to cite this article: Shrivastava, Naira. "Exploring the Impact of Endoplasmic Reticulum Stress on Renal Cell Carcinoma: Navigating an Evolutionary Biology Framework." *J Phylogenetics Evol Biol* 11 (2023): 277.