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Renal Cell Carcinoma Endoplasmic Reticulum Stress

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Introduction

The endoplasmic reticulum is an organelle that plays critical roles in protein synthesis, metabolism homeostasis, and cell signalling. Endoplasmic reticulum stress occurs when cells are damaged and this organelle's ability to perform its normal functions is compromised. Specific signalling cascades are then activated, resulting in the so-called unfolded protein response, which has a profound impact on cell fate. Depending on the extent of cell damage, these molecular pathways in normal renal cells strive to either resolve cell injury or activate cell death. As a result, activating the endoplasmic reticulum stress pathway has been proposed as an intriguing therapeutic strategy for pathologies such as cancer.

Renal cancer cells, on the other hand, are known to hijack these stress mechanisms and use them to their advantage in order to promote their survival through metabolic rewiring, activation of oxidative stress responses, autophagy, inhibition of apoptosis, and senescence. Recent evidence strongly suggests that a certain level of endoplasmic reticulum stress activation is required in cancer cells to shift endoplasmic reticulum stress responses from pro-survival to pro-apoptotic. Several endoplasmic reticulum stress pharmacological modulators of therapeutic interest are already available, but only a few have been tested in the case of renal carcinoma, and their effects in vivo are unknown [1].

Description

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 [2].

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 [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.

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.

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 causes 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].

Conclusion

Finally, in order to proceed with such personalised medicine approaches, the decision to effectively hyperactivate ER stress in RCC or to sensitise RCC to specific treatment by suppressing ER stress signalling must include the determination and standardisation of basal UPR activation levels in patients' tumours. In addition to the traditional analyses of mRNA expression, XBP1 splicing, or protein analyses of total phosphorylated UPR effectors, new standardised procedures and quantitative measures of ER stress in patients' tumours must be developed. This necessitates the development of a standardised multi-parametric activation/inhibition range for the UPR, which would clearly indicate the best ER stress modulation strategy for a given patient.

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Conflict of Interest

There are no conflicts of interest by author.

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