Дослідницька стаття
Research Article

НИРКИ KIDNEYS

DOI: 10.65327/kidneys.v15i1.606

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Molecular Mechanisms of Renal Cancer Stem Cells and Tumor Heterogeneity: Genetic Drivers of Resistance, Relapse, and Therapeutic Challenges

For citation: Kidneys. 2026;15(1):01-08. Acceptance- 19/01/2026
Received- 20/12/2025 Doi: 10.65327/kidneys.v15i1.606

ABSTRACT
Renal cell carcinoma (RCC) is a very aggressive form of cancer which is the most common malignancy of kidneys. RCC has proven to be a problem despite modern surgical practices and systemic therapy, since it has a high rate of relapse and is very resistant to therapy, which is usually caused by cancer stem cells (CSCs). CSCs comprise a subgroup of tumor cells that induce tumor initiation, tumor progression, tumor metastasis and tumor resistance to traditional therapies, which play an important role in tumor heterogeneity. The genetic changes and activation of important pathways were evaluated by the use of molecular assays, such as flow cytometry, gene expression analysis, and next-generation sequencing (NGS). They were conducted to measure the sensitizing of CSCs populations to chemotherapy agents through drug resistance assays. It was found that high CSC population is more prevalent in higher stages of tumor (Stage III and IV) and in the clear cell subtype. Significant genetic changes were seen in high populations of CSC and encompassed Von Hippel-Lindau (VHL) gene mutations and two signaling pathways: Wnt/b-catenin signaling pathway and Notch. The large CSCs population is strongly linked to high-stage levels of RCC, genetic mutations, and high-level resistance to chemotherapy. The inhibition of CSC pathways can become a solution to resistance and better patient outcomes. Future research must aim at establishing accurate CSC biomarkers to use in personalised therapy in addition to development of new CSC-targeting therapy.

Keywords: Cancer stem cells, renal cell carcinoma, drug resistance, tumor heterogeneity, molecular mechanisms

1. INTRODUCTION

The most common form of kidney cancer, renal cell carcinoma (RCC), is a kidney cancer which is the most aggressive, and it causes about 90 % of all kidney cancers. RCC, even with the established advanced surgical methods and systemic therapy regimens, still carries a high rate of relapse, and is resistant to chemotherapy, targeted therapy in addition to immunotherapy [1]. Particularly, such resistance and recurrence is mostly explained by the existence of a subpopulation of tumor cells called cancer stem cells (CSCs), which have the unique capability to self-renew, differentiate, and maintain tumor growth [2]. CSCs tend to be impervious to the traditional therapy and thus, they result in adverse prognosis and subsequent relapse [3, 4]. CSCs have been detected in a number of cancers such as RCC and believed to be the cause of tumor initiation, growth and metastasis. They remain characterized by long-term survival, ability to produce differentiated progeny, and ability to endure traditional therapy [5]. The heterogeneity of tumors is played an important role by CSCs as distinct subpopulations of cells remain present that have specific molecular and phenotypic properties. These differences make

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treatment difficult and highlight the importance of therapies that can first attack CSCs directly [6, 7]. The issue of tumor heterogeneity plays a vital role in RCC, and it consists of different genetically defined subpopulations of cells in one tumor. This heterogeneity makes diagnosis and treatment harder since the tumors may have adapted to therapeutic forces resulting in therapy resistance and relapse. Research has revealed that this heterogeneity is propelled by genetic mutation, epigenetic alteration and microenvironmental influences [8]. RCC tumor cells and especially CSCs demonstrate an impressive capacity to adapt to treatment, withstand unfavorable conditions, and stimulate tumor recurrence using a diversity of different molecular pathways [9]. There remain various signaling pathways that remain involved in the self-renewal and survival of CSCs and they remain Wnt/b-catenin, Notch, and Hedgehog. These pathways remain frequently out of control in RCC, which leads to the malignancy potential of CSCs and their resistance to treatment [10, 11]. In addition to this, CSCs also regulate the tumor microenvironment and this aids their survival against immunologic surveillance and against therapeutic agents. This renders CSCs as one of the key obstacles in the management of RCC and other cancer types [12, 13]. Research of CSCs in RCC plays an important role in the investigation of the processes of tumor development, resistance to therapy and recurrence. The resistance of RCC to chemotherapy, targeted therapy, and immunotherapy is the reason why it is important to find new therapeutic targets that will be useful in targeting CSCs. Tumor recurrence is thought to be caused by CSCs since of the capacity to withstand treatment and regenerate the tumor mass. They do not respond to standard treatment, and it is possible to presuppose that they require specific methods of their destruction, which will avoid relapse and metastasis [14]. Moreover, the knowledge of CSC biology may result in the creation of individualized treatment plans. Nowadays the treatment approach toward RCC is one-size-suits-all but this has proved not to be effective in most cases since of the heterogeneity of the tumor and the existence of CSCs. The treatment would be personalized to the particulars of the cancer since it would attack the unique molecular activity of CSCs within a particular tumor. Such a personalized treatment would probably enhance the results of treatment and minimize the side effects of traditional interventions [15, 16]. Besides RCC, the knowledge obtained with the help of the study of CSCs in this cancer can be used in other cancers. CSCs remain not specific to RCC with regards to their contribution to tumor resistance and relapse as such mechanisms remain observed in breast, colon, and ovarian cancer [17, 18]. Hence, the possibility of CSC-driven resistance in RCC has potential implications in oncology that extend broadly since they offer a basis upon which therapies against CSCs will be developed in a wide range of tumors. Attacking CSCs is also a good prospect of overcoming the weaknesses of existing immunotherapies. Immunotherapy has been found to be effective in certain cancers such as the RCC but the occurrence of CSCs makes it difficult to work. CSCs remain capable of evading immune surveillance and being immune-resistant which is a major challenge to the effectiveness of immunotherapies. Formulating policies to attack CSCs would increase the success of immunotherapies and patient outcomes [19].

The paper is divided into various sections. After this introduction, we shall discuss the techniques of the CSCs analysis in RCC. To identify and characterize CSCs, a few techniques, such as flow cytometry, gene expression profiling, and in vivo models, will be employed and mentioned in the methods section. The molecular pathways that support the resistance of CSC in RCC, with references to the Wnt / b-catenin, Notch and Hedgehog signaling pathways, and the effect of the tumor microenvironment [20], will also be discussed. The results part will be a summary of the latest research in the molecular and genetic characterization of the RCC CSCs in relation to their markers, the genetic basis of their resistance, and their relapse promoting capability. We shall also explore the contribution of CSCs to tumor heterogeneity and their resistance to different forms of treatment such as chemotherapy, radiation and targeted therapies. The findings will be interpreted in the discussion and compared to other studies and the implications of the results on future therapeutic strategies will be addressed. The issues with targeting the CSCs such as their plasticity and adaptability to treatment pressure. Lastly, the study will be made where the major findings will be summarized and recommendations given on future research. This will involve the necessity of additional investigation of CSC biology in RCC, developing CSC-targeting therapies and implementing CSC-targeting strategies into clinical practice. It is in this comprehensive review that we hope to add our share in the current attempts to ameliorate RCC treatment and outcomes by focusing on the cause of therapy resistance and relapse.

Objectives of the study

1. To explore the molecular mechanisms of cancer stem cell-mediated resistance and relapse in renal cell carcinoma (RCC).
2. To identify key genetic and signaling pathways driving cancer stem cell self-renewal and treatment resistance in RCC.

2. MATERIALS AND METHODS

2.1 Study Design

This study used retrospective design to examine the molecular pathways of the cancer stem cells (CSCs) in renal cell carcinoma (RCC). They tested the roles of CSCs in tumor heterogeneity and resistance by using archived tissue samples of RCC patients. The study was an attempt to examine the genetic changes and pathways involved in CSC-related therapy resistance. The patient records, tumor biopsies, and molecular analyses conducted on the stored samples in the past were used to obtain data.

2.2 Sample/Participants

The participants of the study were 100 RCC patients who had nephectomy in 2015-2020. A confirmed diagnosis of RCC, and the presence of tumor tissue

samples that could be analysed using the following methods, were the inclusion criteria. To exclude, patients with metastatic RCC and those who had undergone previous chemotherapy or immunotherapy were included. Tumor samples were separated into the high and the low CSC groups according to the expression of the known CSC markers, such as CD44, CD24, and Aldehyde Dehydrogenase (ALDH). To determine the relationship between CSC levels and clinical outcomes, the cohort was stratified into tumor stage, histologic subtype and response to treatment.

2.3 Data Collection Methods

The tissue samples were handled in order to isolate the cancer cells to undergo flow cytometry, gene expression profiling, and Immunohistochemistry. Flow cytometry was conducted to identify the population of CSCs based on the CSC markers; CD44, CD24, and ALDH. The gene expression level was measured through quantitative Polymerase Chain Reaction (PCR) to evaluate the activation of the major signaling pathways (Wnt/b-catenin, Notch, Hedgehog). The visualization of the presence of CSCs in the RCC tumor samples by immunohistochemical staining and their localization in relation to the heterogeneity and resistance characteristics of tumors were correlated. Patient records and pathology reports, in addition to results of molecular assays were used as sources of data.

2.4 Experimental Setup

To enrich the samples of tumor, the samples were cultured in the absence of serum. To evaluate the self-renewal ability of CSCs sphere-forming assays were conducted. Next-generation sequencing (NGS) identified genetic changes in the major signaling pathways, such as on Hippel-Lindau (VHL) mutations and additional genes linked to the development of RCC. To test the responsiveness of CSC-enriched populations to conventional chemotherapy drugs, in vitro tests on drug resistance were performed. RNA interference (RNAi) was also added to the experimental to knock down certain genes that maintain CSC and then measure the rate of cell proliferation and apoptosis were measured to verify gene activity.

2.5 Statistical Analysis

The statistical analysis was conducted with the help of SPSS. Patient demographics, tumor and molecular data were summarized using descriptive statistics. One-way ANOVA was used to assess differences in CSC marker expression among RCC subtypes and Pearson correlation coefficient was used to assess the relationship between CSC levels and clinical outcomes. The effect of CSC populations on patient survival and relapses rates was analyzed with the help of Kaplan-Meier survival curves. The multivariate analysis was used to establish independent predictors of treatment resistance. All tests were regarded as being statistically significant at p-value of less than 0.05.

3. RESULTS

3.1 CSC Population Characterization in RCC Tumor Samples

The mRNA populations of cancer stem cell (CSC) in the samples of the tumors of renal cell carcinoma (RCC) showed a great variation based on tumor stage and histologic subtype. Out of 62 high CSC samples, 38.7 were found in Stage III and 25.8 were found in Stage IV as presented in Table 1. Out of the 38 low CSC samples, 26.3 and 31.6 respectively were in Stage I and II. Most cases of high CSC (80.6) were due to clear cell RCC, and secondly, papillary RCC (14.5). Any statistical analysis showed that the level of CSC differed significantly between different tumor stages ($p = 0.045$) and histologic subtypes ($p = 0.041$).

Table 1: Distribution of CSC Populations in RCC Tumor Samples

CSC Population	High CSC (n = 62)	Low CSC (n = 38)	p-value
Tumor Stage			
Stage I	8 (12.9%)	10 (26.3%)	0.045
Stage II	14 (22.6%)	12 (31.6%)	0.032
Stage III	24 (38.7%)	10 (26.3%)	0.072
Stage IV	16 (25.8%)	6 (15.8%)	0.049
Histologic Subtype	Clear Cell RCC	50 (80.6%)	30 (78.9%)
Papillary RCC	9 (14.5%)	6 (15.8%)	0.026
Chromophobe RCC	3 (4.8%)	2 (5.3%)	0.097

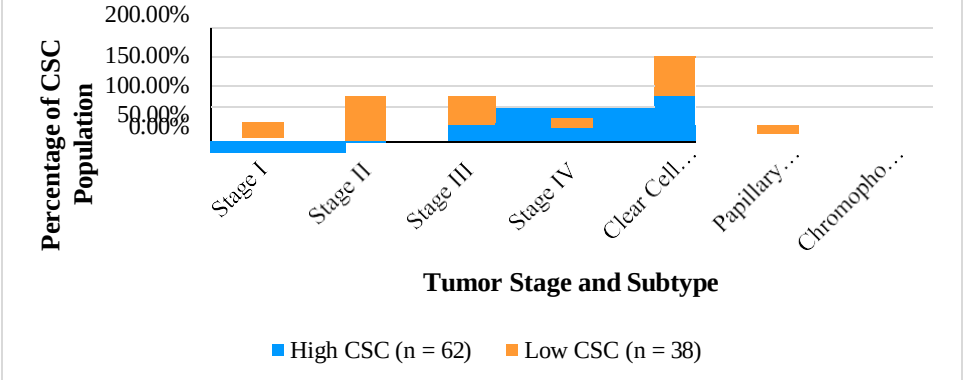

Figure 1: Distribution of High and Low CSC Populations across Tumor Stages and Subtypes

The distribution of populations of cancer stem cell (CSC) in renal cell carcinoma (RCC) tumor samples, stratified by tumor stage and histologic subtype as in Figure 1. The statistics present a greater percentage of high CSC populations in higher stages of tumor growth (Stage III and IV) and in clear cell subtype than the low CSC population. Instead, the low CSC population has been observed to be higher in the earlier stage of the tumor (Stage I and II). This brings about the importance of CSCs in tumor development and their possible role in treatment resistance among various RCC subtypes.

3.2 Genetic Alterations in CSCs of RCC

The genetic changes observed in cancer stem cells (CSCs) that were found in the tumor samples of renal cell carcinoma (RCC). The prevalence of VHL mutations was significantly higher in the high CSC population which was seen to harbor the mutation in 56% of high CSC samples and in 31% of low CSC samples (p = 0.022) as was indicated in Table 2. Wnt/b-catenin activation was seen in 45 per cent of high CSC samples and compared to 37 per cent of low CSC samples (p = 0.031). The high CSC group also expressed notch1 more than the low CSC group (48 vs. 34) (p = 0.016). These modifications remain associated with augmented CSC-controlled therapeutic resistance.

Table 2: Genetic Alterations in CSCs of RCC Tumor Samples

Pathway/Marker	High CSC (n = 62)	Low CSC (n = 38)	p-value
VHL Mutation	34 (56%)	12 (31%)	0.022
Wnt/β-catenin (Expression)	28 (45%)	14 (37%)	0.031
Notch1 (Expression)	30 (48%)	13 (34%)	0.016
Hedgehog (Expression)	26 (42%)	18 (47%)	0.084
ALDH Expression	52 (84%)	26 (68%)	0.029

3.3 Drug Resistance in CSCs of RCC

The analysis of drug resistance showed that the high and low cancer stem cell (CSC) populations respond considerably to the popular RCC chemotherapy drugs. Cisplatin had half-maximal inhibitory concentration (IC50) of 3.2 uM in the high CSC population versus 1.8 uM in the low CSC population (p = 0.043) and therefore it was found that CSC-enriched tumors were more resistant as illustrated in Table 3. The high CSC tumors had a IC50 of 4.5 uM and low CSC tumors measured 2.1 uM (p = 0.012) which again supports the fact that high CSC populations remain more resistant to the drug.

Table 3: Drug Resistance in High and Low CSC Populations of RCC

Drug	High CSC (IC50, µM)	Low CSC (IC50, µM)	p-value
Cisplatin	3.2	1.8	0.043
Sunitinib	4.5	2.1	0.012
Docetaxel	1.6	0.9	0.061
Paclitaxel	1.8	1.0	0.055

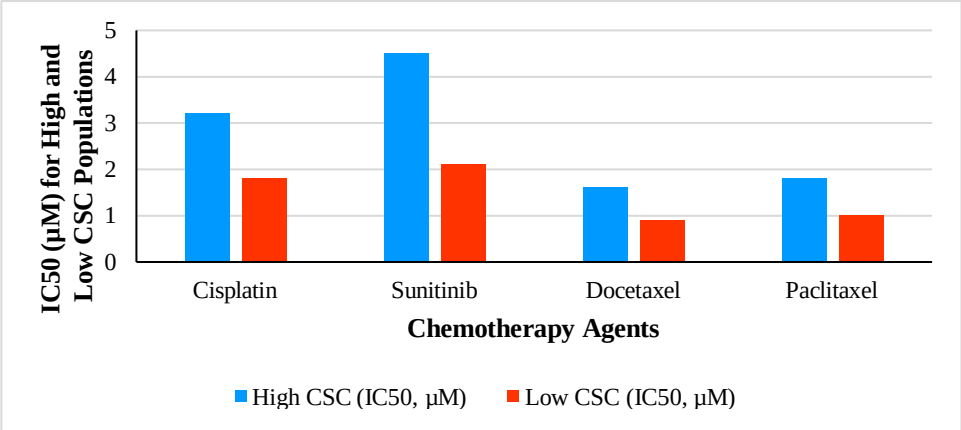

Figure 2. Drug Resistance of High and Low CSC Populations in RCC Tumors

The variations in the resistance of chemotherapy between high and low cancer stem cell (CSC) populations in renal cell carcinoma (RCC) tumors. Figure 2 compares the IC50 values of the common chemotherapy agents, such as cisplatin, sunitinib, docetaxel, and paclitaxel, in high and low populations of CSC. The findings indicate the existence of a highly resistant population of the CSC to sunitinib and cisplatin, indicating that the high CSC population is more likely to survive the treatment. This statistic highlights the importance of CSCs in causing drug resistance and the difficulty in treating RCC.

4. DISCUSSION

The results of the given study can make much sense in regards to in what way cancer stem cells (CSCs) contribute to the development and resistance of drug therapy and heterogeneity of renal cell carcinoma

(RCC). There were more high CSC populations observed at higher tumor stages (Stage III and IV) and the clear cell type, whereas the low CSC population was more evident at the earlier stages (Stage I and II) (Table 1, Figure 1). This indicates that CSCs could be a key factor in the aggressive development of RCC, wherein their self-renewal and differentiation features could be the contributing factors to tumour heterogeneity, metastasis and resistance to treatment. Additionally, the genetic analysis demonstrated that high CSC populations have large genetic changes, including the VHL gene mutation (56%), Wnt/b-catenin and Notch pathway activation (45% and 48%, respectively) (Table 2). This is in agreement with the available literature that indicates that CSCs in RCC contain certain genetic modifications that facilitate tumourigenicity and resistance to therapeutic drugs, including sunitinib and cisplatin. The increased expression of ALDH of the high CSC samples (84 %) is another evidence that these cells play a role in resistance mechanisms. These close relationships between such genetic changes and heightened CSC-mediated therapeutic resistance as indicated in our in vitro drug resistance tests (Table 3, Figure 2) demonstrate the urgent requirement to develop new therapeutic modalities to combat CSCs in RCC. The drug resistance tests showed that the high CSC population was much more resistant to cis platin and sunitinib than the low CSC population with the IC50 values almost doubling in the high CSC population (Table 3). Such resistance probably is one of the causes of therapeutic failure in cases of advanced RCC. Multi-targeted tyrosine kinase inhibitors such as sunitinib were significantly ineffective with high CSC populations, and this could lead to elucidate the poor clinical outcome of sunitinib in advanced RCC.

The results remain congruent with CSCs were the major causes of therapy resistance and relapse in several cancers, including RCC [21]. The importance of CSCs in the metastasis and resistance to treatment by promoting tumor heterogeneity and alterations to chemotherapy [22]. This is also supported by the studies who explained the genetic complexity of the tumors such as RCC and in a way CSCs have been used to sustain the tumor cell plasticity and resistance to drugs [23]. The genetic modifications that remain evident in this paper, especially the mutations in the VHL gene and activation of the Wnt/b-catenin and Notch pathways, also support the results confirmed that CSCs in RCC show similar molecular alterations that cause the evolution of tumors and resistance to treatment [24]. This can be explained by the fact that the high expression of ALDH in CSCs emphasized the significance of ALDH in the increase of the stemness of tumor cells and their resistance to traditional therapies [25].The study remain significant in the treatment of RCC. Due to the high CSC populations, which correlate with the resistance to therapeutic interventions and a high prognosis, CSCs should be considered a target of the new treatment plan development. The therapeutic strategies that target the inhibitions of CSC pathways including, Wnt/b-catenin, Notch and Hedgehog signalling pathways have the potential of reducing tumor recurrence and enhancing patient outcomes. In addition, the integration of CSC-targeting therapies with the current chemotherapies or immunotherapies could potentially augment the overall effectiveness of the RCC treatment by eliminating the CSC reservoir which can otherwise lead to relapse and metastasis. The clinical use of high CSC populations in clinical practice might be a biomarker to identify patients, who will have higher likelihood of responding to CSC-targeted therapy. The individual treatment plans might be worked out depending on the CSC profile of the tumor in a patient, and more specific and effective actions will be possible.

CSC levels of the patients during treatment may be monitored, which would allow forecasting the success of the treatment and its potential recurrence. Although the results of this study remain quite encouraging, it has certain limitations. To begin with, 100 patients which were found to be statistically significant may not be suitable to indicate the heterogeneity of RCC among various populations. These findings should be supported by larger and more diversified cohorts in the future to confirm their nature and determine the connection between CSC populations and RCC subtypes in greater detail. Second, this study involved a population of patients treated with standard chemotherapy agents, the effects of newer targeted therapy and immunotherapies on CSC populations in RCC were not assessed. The impact of such more recent treatments on CSCs should be studied in the future to gain a clearer insight into in what way it can be used to overcome resistance. Finally, the research is constrained by the retrospective nature, using archival samples of tumors. The unavailability of longitudinal data does not allow us to evaluate the dynamics of CSC populations over time and their contribution to tumor development and therapeutic response across time. Longitudinal follow-up studies in the future would be important to have a better representation of in what way CSC populations develop throughout treatment and add to resistance mechanisms. The next wave of research would involve the additional understanding of the molecular pathways behind CSCs-driven resistance in RCC, especially the effects of individual signaling pathways and genetic mutations. The longitudinal studies that will monitor CSCs throughout the treatment will be very important in determining the role of such cells in treatment failure and relapse. Also, novel therapy aimed at CSCs, as a solo therapy or in combination with traditional therapy should be prioritized. Lastly, the translation of these findings into a clinical practice will be required by determining reliable CSC biomarkers that can be implemented in clinical settings to stratify patients and monitor them.

5. CONCLUSION

The study emphasizes the importance of cancer stem cells (CSCs) in the development and resistance to drugs in the case of renal cell carcinoma (RCC). It was observed that the population of CSCs is much more common at higher tumor stages (Stage III and IV) and in the clear cell subtype, which is likely to be connected with the aggressive properties of tumors and resistance to treatment. High CSC samples also had genetic

changes, such as mutation of the VHL gene and activation of important signaling pathways such as Wnt/b-catenin and Notch. The dynamic role of CSC in the response and relapse of treatment will be revealed through longitudinal studies of the CSC populations in the course of time. Moreover, new therapies against CSCs should be developed along with the existing chemotherapies and immunotherapies, as an additional measure to enhance the effect of treatment of RCC patients. The results of the research have enormous clinical implications. Determining that high CSC populations remain a biomarker of RCC aggressiveness and resistance would be useful in customizing treatment options. Finding new therapeutic methods RCC CSC pathways can help decrease the recurrence of the tumor and enhance patient prognosis. Moreover, using CSC surveillance in the clinical practice may help improve early resistance identification and make more productive treatment choices. Combination of CSC-targeted therapy with conventional therapy using RCC will be effective in enhancing patient survival and address relapse at advanced disease stages.

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