

Correlation analysis between renal clear cell carcinoma and BAP1

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Abstract: Renal clear cell carcinoma (ccRCC) is the most typical pathological type of renal carcinoma (RCC), accounting for about 75%. The pathogenesis of ccRCC is a complex process in which multiple factors or multiple gene variations act together and affect each other. With the deepening research of ccRCC and the development of next-generation sequencing, genomics has been recognized and widely used in cancer research. At present, the mutant gene map of renal clear cell carcinoma has been obtained by high-throughput targeted sequencing, in which the mutant gene BAP1 is a typical tumor suppressor gene. Studies have found that the mutation of BAP1 is closely related to the development and progression of ccRCC. BAP1 mutation is ubiquitous in ccRCC, and has attracted more and more scholars' research interest. Fruitful research results have been obtained, which is of great significance for the early diagnosis and targeted therapy of ccRCC. BAP1 may play a protective role in the development of CCRCC, and its mutation is a marker of poor prognosis in CCRCC. The pathogenesis, proliferation, biological activity, clinical stage and prognosis of renal clear cell carcinoma are all related to the expression and function of BAP1. BAP1 plays an important role in the development of renal clear cell carcinoma.

Keywords: Renal clear cell carcinoma, gene mutation, BAP1 gene sequencing

1. Epidemiology of renal clear cell carcinoma

Renal clear cell carcinoma is a very common malignant tumor in the urinary system which is from the renal parenchyma urinary tubular epithelial system. Its incidence rate accounts for about 85% of the primary renal cancers and 2% ~ 3% of the malignant tumors, the fatality rate is also the highest in the malignant tumor of urinary system. The incidence of all stages of this cancer has increased over the years, resulting in a steady increase in mortality per unit of the population. The male to female ratio was 2:1 in patients with clear cell carcinoma of the kidney. The peak age of onset was between 60 and 70 years old (mean age is about 64 years old), and the median age at diagnosis was 64 years. Surgical resection is an effective treatment for early renal clear cell carcinoma. With high invasiveness of renal clear cell carcinoma, which usually metastasizes to the lungs, lymph nodes, lungs, adrenal glands, brain, and bone, patients with metastatic renal clear cell carcinoma have a 5-year survival rate of less than 10% [1-3]. And 30% of patients with localized clear cell carcinoma of the kidney will have postoperative recurrence at different times. The prognosis of these patients with postoperative recurrence or metastasis of clear cell carcinoma of the kidney is very poor, and the 5-year survival rate of some patients is less than 25%. However, the treatment of advanced or recurrent renal cell carcinoma is very limited, and the effect of chemotherapy and radiotherapy is not good [4-5]. Although the development of targeted therapies and immunotherapy modalities has prolonged the survival of patients with ccRCC in recent years, most patients with long-term use of molecularly targeted drugs develop drug resistance [6]. The overall prognosis of renal cell carcinoma patients is still not optimistic.

At present, for patients with advanced and metastatic renal clear cell carcinoma, it is impossible to achieve individualized and precise treatment by only relying on pathological type to design the treatment regimen and therapeutic drugs for patients with tumor. In addition to considering the basic characteristics of a patient's medication, it is important to address the root causes of the problem and block the progression of the tumor. The genetic characteristics of the tumor open the door to precision treatment. The emergence of genetic defects is usually a critical step in the development of tumors and always occurs in the early stages of tumor formation. The clinical outcomes of patients with clear cell carcinoma of the kidney vary widely, but now we know little about the molecular genetics that contribute to these different clinical outcomes. Recently, with the development of high-throughput sequencing technology, rapid breakthroughs have been made in the study of cancer mutation mapping and cancer genomics.

However, the gene mutation mapping characteristics and molecular functional mechanisms of renal clear cell carcinoma have been gradually perfected, it is urgent to analyze the clinical features and prognosis of the gene-mutated clear cell renal cell carcinoma, so as to provide the theoretical basis and the basis of translational medicine for the precision medicine of clear cell renal cell carcinoma, which has important clinical significance and social value.

2. Progress in gene sequencing of renal clear cell carcinoma

The Cancer Genome Atlas (TCGA) identified a number of genes with high frequency mutations in renal clear cell carcinoma by high-throughput and large-sample sequencing of the genome and exons of renal clear cell carcinoma samples [7]. There are two general types, one is chromatin epigenetic regulators, the other is ubiquitin-mediated protein degradation pathway-related factors, including BAP1, TCEB1, Cul7 and BTRC. BAP1 was mutated in 15% of clear cell renal clear cell carcinomas, ranking the third, only next to VHL and PBRM1[8]. The next generation sequencing technology was used to screen the somatic mutation of clear cell carcinoma of kidney-related genes, which expanded the somatic mutation spectrum of the susceptible genes of clear cell carcinoma of kidney. It is very important to identify the mutated genes for finding specific therapeutic targets.

Previous studies have shown that BAP1 mutations occur in about 15% of patients with clear cell renal cell carcinoma, and the sequencing work showed that BAP1 mutation had a great impact on the occurrence, development, proliferation, invasion and prognosis of patients with clear cell renal clear cell carcinoma. Germline mutations in the BAP1 gene have been identified as a hallmark gene of the tumor susceptibility syndrome (TPDS) in many cancers, which increases the risk of cancers such as melanoma, renal clear cell carcinoma, malignant mesothelioma, and others [9]. BAP1 is a tumor suppressor. When the tumor suppressor gene is mutated, it may lead to the occurrence of tumor. At present, there are many researches on the mechanism of development of BAP1 and clear cell carcinoma of kidney in China, but the summary of clinical features and prognosis evaluation is not enough. Otherwise, it will be possible to provide new therapeutic schemes and prognostic monitoring indexes for patients with this gene mutation.

3. Basic BAP1 information

BAP1 is located at 3p21. 1, which encodes a protein BAP1 made up of seven hundred and twenty-nine amino acids. BAP1 consists of Ubiquitin c-terminal hydrolases (Uch) domain (nos. 1-250 AA), HCF-1-binding domain (HBM) (nos. 363-366 AA), and two-part Nuclear localisation signal (NLS) (nos. 656-661 AA and 717-722 AA) [10-11]. BAP1 encodes an 80. 4KD nuclear localization protein and ubiquitin carboxyl-terminal hydrolase (UCH) domain enable Bap1 to produce deubiquitinase activity [12].

BAP1 is a BRCA1-associated protein 1(BAP1), which has been found to be associated with the development and progression of clear cell and renal clear cell cancers in recent years [13]. Experimental results suggest that somatic BAP1 mutations can lead to normal expression of apoptotic process cell death-Ligand 1(PD-1) in ccRCC cells [13]. The structure and function of BAP1 and the role of BAP1 mutation in the occurrence and development of ccRCC. This ubiquitin removal can achieve a variety of functions, such as participating in transcriptional regulation, epigenetic regulation, DNA damage repair, etc., to understand the occurrence and development mechanism of ccRCC. BAP1 mutation plays an important role in ccRCC [14-15]. Exploring the correlation between BAP1 and renal clear cell carcinoma has become an important issue, which lays a theoretical foundation for guiding the treatment and prognosis of renal clear cell carcinoma.

4. Research on BAP1 in other tumors

Researchers have found that BAP1 promotes the growth of breast cancer cells by controlling the deubiquitination of KLF5[16]. BAP1 is involved in multiple cellular pathways associated with the development and progression of malignancy, and recent studies have also confirmed the discovery of BAP1 somatic mutations in breast and lung cancer cell lines; Zhongtong et al. constructed a hepatoma cell line with stable knockout and overexpression of BAP1, dissecting the negative effects of BAP1 biological properties, and constructed a nude mouse subcutaneous tumor model [17]. Hirsch et al. analyzed 151 liver tumors by using RNAseq and whole-genome or whole-exome sequencing techniques

and identified BAP1-driven subgroups of HCC with fibrous features and dysregulation of the PKA pathway [18]. Recently, BAP1 mutations have attracted much attention in oncology, including clear cell renal cell carcinoma (RCC).

5. The relationship between BAP1 and the etiology of renal clear cell carcinoma

The tumor suppressor genes VHL, PBRM1 and SETD2 of all CCRCC except BAP1 are located on the short arm of the chromosome 3. The production of ccRCC is associated with VHL gene mutation with 3p deletion, and the VHL mutation rate is the highest. VHL mutation occurs in more than 70% of sporadic ccRCC patients, the mutation rates of the other two genes were 40% (PBRM1) and 16% (SETD2) [4]. Although the mutation rate of VHL and PBRM1 was higher, the mice with VHL and PBRM1 gene knockout did not form ccRCC or other pathological types of renal cell carcinoma, but the mice with VHL-BAP1 homozygous deletion showed renal cell carcinoma or precancerous lesion, and mice were lethal within a month. Gao et al. (2017) analyzed mice with dual knockout of VHL-BAP1, PBRM1-BAP1 associated with a CCRCC model, all of which were available; These results suggest that BAP1 may be a more important RCC suppressor gene than VHL and PBRM1 [19-20].

6. The correlation between BAP1 and pathology of renal clear cell carcinoma

HAT1 expression was elevated after knockdown of BAP1 in renal clear cell carcinoma cell lines, which promoted the proliferation and invasive ability of renal clear cell carcinoma cells in part through the elevation of HAT1 expression; BAP1 and HAT1 genes in clear cell renal cell carcinoma (RCC) had significantly positive effects on the pathological parameters of Furhman grading and advanced PT staging.

HCF1 (Host cell factor1) interacts strongly with BAP1. HCF1 is an important regulator of the cell cycle and contains a Kelch domain capable of binding to the HBM (HCF1-binding motif) conserved on other proteins. BAP1 influences transcriptional processes through deubiquitination of histone H2A and HCF1, thereby regulating cell cycle and inhibiting cell proliferation [21]. Thus, abnormal BAP1 function results in the loss of the ability to inhibit cell proliferation, thus promoting the occurrence of ccRCC. Studies have shown that BAP1-mutated renal clear cell carcinoma is more aggressive and has a relatively poor prognosis [22].

7. The relationship between BAP1 and the treatment of renal clear cell carcinoma

The study conclusion [23] showed that BAP1 deletion increases the sensitivity of renal clear cell carcinoma to radiotherapy and reflects impaired ability of tumor cells to repair double-stranded DNA damage induced by stressors. In different cancer cells, BAP1 results in differences in sensitivity to chemotherapeutic agents in cancer cells. Because renal clear cell carcinoma is less sensitive to radiation therapy than other cancers, there is no studies have shown whether new radiotherapy regimens for renal cell carcinoma are available at present.

8. The relationship between BAP1 and the prognosis of renal clear cell carcinoma

The prognosis of patients with renal clear cell carcinoma is mainly influenced by the degree of anatomical progression and histological TNM grading. After BAP1 mutation or low expression, the proliferation and invasion of renal clear cell carcinoma cells are partially promoted by HAT1 [24], which is prone to adverse pathological features and invasive lesions. BRCA1-mediated ubiquitination and BAP1-mediated deubiquitination can effectively coordinate and control the proliferation process of tumor cells. In renal clear cell carcinoma, it is precisely because of BAP1 mutation that the expression level of BAP1 is reduced, resulting in an inhibitory effect on the production of cancer cell growth and thus promoting the proliferation of renal clear cell carcinoma [25]. Previous investigations [26] have shown that patients with weakly BAP1-positive and BAP1-positive renal clear cell carcinoma have a significantly increased risk of specific death. Therefore, the overall survival time of BAP1 mutant patients is significantly different from that of PBRM1 mutant patients.

For renal clear cell carcinoma, although there are many comprehensive diagnostic methods that can improve the prognosis of patients, however, the study of biomarkers with important clinical significance is still the key measure to improve the treatment condition and prognosis of patients, especially for the

evaluation of the prognosis of malignant tumors, will help to distinguish between the nature and characteristics of cancer [27].

9. The double mutation of BAP1 and BRCA1 cause abnormal DNA damage repair pathway

DNA damage repair plays an important role in maintaining the integrity and stability of genomic sequence information and carcinogen generation. DNA damage is achieved by activating the complex and sophisticated DNA damage response (DDR) pathway [28], and aberrant DNA repair can cause carcinogenesis. With the recent advances in cancer research, there is increasing emphasis on the importance of identifying molecular markers to predict treatment response and outcome to achieve precision tumor therapy. Assuming that tumor patients with long non-specific progression survival have "specific biological characteristics", that is, sensitivity to systematic treatment and long-lasting tolerance to response, then the change of DNA damage repair pathway and anti-cancer immunity may form an abnormal response to standard anti-cancer treatment [29].

DNA double strand breaks damage repair (DSBs) may be repaired by homologous or non-homologous recombination. Remarkably, at least seven genes encoding proteins are involved in the repair of DNA double-strand breaks in humans, namely, the DNA-PK gene, the XR-1 gene, the XRCC1 gene and the BRCA1 gene [30], the BRCA1 gene is located on human chromosome 17q12-21, which encodes a number of sites that interact with other proteins and realize important biological effects through the interaction between proteins, including cell cycle regulation, DNA damage repair, gene transcription regulation, apoptosis and ubiquitination, and so on.

BAP1 and BRCA1-BARD1 (BRCA1 associated RING DOMAIN1, Bard1), a DNA damage repair and tumor suppressor complex, regulate each other, and the BRCA1-BARD1 tumor suppressor complex has E3 ubiquitin ligase activity. BAP1, due to its deubiquitination function, deubiquitylates Bard1, which in turn reduces the E3 ubiquitin ligase activity of BRCA1-BARD1, thus having a cancer-suppressing effect. Because shRNA blocks the DNA damage repair function of BAP1 and sensitizes HeLa cells to ionizing radiation, S phase is delayed. Thus, BRCA1-mediated ubiquitination and BAP1-mediated deubiquitylation can co-assist and perform DNA damage repair. BAP1 is phosphorylated after DNA destruction and drives it to aggregate at DNA double-strand breaks (DSB) sites to achieve H2A deubiquitination and controls the recruitment of downstream DNA double-strand break signaling and repair proteins, further helping cells recover from DNA damage. At the same time, because of BAP1 deletion, checkpoint information transmission defects can also lead to damaged DNA-containing cells to survive, and thus promote cancer generation. Furthermore, Eletr et al. suggested that loss of BAP1 alters mRNA expression amounts of some proteins, which comprise subtypes of DNA replication and DNA repair. The knockdown of BAP1 results in a decrease of BRCA1/RAD51 at the site of DNA Double-strand breaks. DNA damage repair protein 51 (RAD51) is a key component of DNA damage repair and plays a key role in ensuring gene stability. The interaction between BRCA1 and many proteins involves in gene transcription, DNA damage repair and so on.

10. Conclusion

The high-throughput targeted sequencing of the mutant gene profiles of renal clear cell carcinoma at home and abroad provides a basis for the diagnosis and treatment of renal clear cell carcinoma in the future. BAP1 mutation is associated with the occurrence and development of renal cell carcinoma, which can be used as a marker for the prognosis of renal cell carcinoma and provide an auxiliary method for the diagnosis and treatment of renal cell carcinoma.

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