International Journal of Trend in Scientific Research and Development (IJTSRD)
Volume 3 Issue 6, October 2019 Available Online: www.ijtsrd.com e-ISSN: 2456 – 6470

Characteristics of Ovarian Cancer: Metabolic Abnormality of Ovarian Clear Cell Carcinoma

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ABSTRACT

Hepatocyte nuclear factor 1β (HNF1β) is expressed only in ovarian clear cell carcinoma (OCCC) and is characteristic of OCCC. This phenomenon is a unique feature of OCCC, including resistance to chemotherapy. However, the biological role of HNF1β in OCCC is not clearly understood yet. Comprehensive metabolomic analysis using the stable cell lines transfected with HNF1β-shRNA showed that HNF1β dramatically changes intracellular metabolism, in particular, induction of aerobic glycolysis, the so-called "Warburg effect". Only when the supply of glucose is enough, HNF1β causes metabolic changes and is thus involved in cell survival under stress such as hypoxia and chemical reagents. Enhanced cell survival is based on a reduction in ROS activity resulting from metabolic changes such as the transition from oxidative phosphorylation to glycolysis and an increase in the intracellular antioxidant glutathione (GSH). One of the cystine transporters, rBAT, may be involved in increasing GSH. These data indicate that HNF1β induced in the endometriotic cyst microenvironment confers a survival advantage on epithelial cells. In other words, the expression of HNF1β is considered to be the cause of OCCC chemotherapy resistance.

KEYWORDS: *Quality of life, Psychological well-being, Elderly, Old age homes, families*

How to cite this paper: Takuma Hayashi | Ikuo Konishi "Characteristics of Ovarian Cancer: Metabolic Abnormality of Ovarian Clear Cell Carcinoma" Published in International Journal of Trend in Scientific Research and Development (ijtsrd), ISSN: 2456-6470, Volume-3 | Issue-6, October 2019, pp.1039-1040, URL: https://www.ijtsrd.com/papers/ijtsrd29308.pdf

IJTSRD29308

Ovarian cancer is a gynecological malignant disease with the poorest prognosis. In Japan, it is said that there are about new 8000 patients per year. Ovarian cancer is a diverse disease both histologically and molecularly. Serological cancer is the most common histologically, and there are other histological types such as endometrioid cancer, clear cell cancer, and mucinous cancer. Ovarian cancer is called a silent killer. When diagnosed, more than 40% are already at stage III or higher. In particular, about 70% of serous cancers are diagnosed at stage III or higher. On the other hand, clear cell carcinoma is the second most common clear cell carcinoma in Japan, accounting for about 25% of ovarian cancer, and about 65% are diagnosed in stage I. Thus, clear cell carcinoma has a different character from common serous carcinoma. The 5-year survival rate for stage I is about 80% for both serous and clear cell carcinomas. However, the 5-year survival rate for stage IV is about 40% for serous cancer and about 25% for clear cell carcinoma, which has a poor prognosis. This is thought to be because clear cell carcinoma is resistant to anticancer drugs [1,2]. In addition, as its name suggests, clear cell carcinoma has a morphological feature that stores glycogen in the cytoplasm and has a clear cytoplasm. Clear cell carcinoma is often associated with endometriosis, and in our hospital cases more than 80% of clear cell carcinomas have endometriosis [3,4]. Clear cell carcinoma often involves blood clots and causes Trousseau syndrome. In our hospital, why does ovarian clear cell carcinoma store glycogen, why does ovarian clear cell carcinoma have anticancer drug resistance, we are investigating these issues by focusing on the environment where clear cell carcinoma is associated with endometriosis.

Endometriosis that occurs in the ovary causes bleeding during menstruation, creating a hemorrhagic cyst, which becomes an ovarian endometriotic cyst. It is also called a chocolate cyst because the liquid is chocolate-colored due to old blood. We focused on the content of ovarian endometriotic cysts, especially iron in the blood. When measuring the iron concentration of the liquid, it was found that the content of free iron was significantly higher in the fluid of endometriotic cysts compared to other benign ovarian cysts. Free iron causes an oxidation-reduction reaction called Fenton reaction ($Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH\cdot + OH^-$, $Fe^{3+} + H_2O_2 \rightarrow Fe^{2+} + OOH\cdot + H^+$), and generates oxidative stress such as hydroxy radical and hydroperoxide radical. In addition, 8-hydroxy-2'-deoxyguanosine (8-OHdG), a marker of DNA damage due to oxidative stress, is abundant in the content fluid of intimal cysts. It was found that 8-OHdG is also present in many endometriosis epithelial cells. Clear cell carcinoma has more 8-OHdG in the cancer cell than serous carcinoma, clear cell carcinoma was found to grow even in an oxidative stress environment.

When we examine the growth environment of clear cell carcinoma, 320 genes that are characteristic of clear cell carcinoma; Ovarian Clear Cell Carcinoma signature (OCCC signature) was identified [5,6]. This gene group contains

many oxidative stress-related genes, glycogen-related genes, and coagulation-related genes, indicating that the nature of clear cell carcinoma is reflected [5,6]. It was also found that a gene network centered on hepatocyte nuclear factor-1-beta (HNF1B), which is highly expressed in clear cell carcinoma, has been constructed. Interestingly, it was found that iron stress and oxidative stress induce the expression of the OCCC signature gene. This physiological phenomenon suggests that the nature of clear cell carcinoma is based on the developmental environment. The transcription of HNF1B was also regulated by DNA methylation.

This mutation in the *HNF1B* gene is known to cause maturity-onset diabetes of the young, subtype 5 (MODY5) [7,8]. Therefore, we examined the nature of clear cell carcinoma by focusing on glucose metabolism. In the ovarian clear cell carcinoma cell line, in which expression of HNF1B was artificially suppressed, the expression of glucose transporter type 1 (GLUT1) was suppressed and glucose uptake was suppressed. This is known as the Warburg effect and reflects the characteristic of cancer cells that anaerobic glycolysis is enhanced even in an aerobic environment, HNF1B also promotes the synthesis of glutathione, known as an antioxidant, via related to b0,+ amino acid transporter (rBAT), a cystine transporter. It has been found that the reactive oxygen species in the cells are reduced to show resistance to iron stress and anticancer drugs [9].

Unfortunately, there are no molecularly targeted drugs that target HNF1B or rBAT. However, we focus on a molecule called pyruvate dehydrogenase kinase isoform 2 (PDK2) that controls the function of mitochondria in which the Warburg effect and tricarboxylic acid (TCA) cycle work. The experiments with mice have shown that controlling mitochondrial function increases the sensitivity of anticancer drugs. In the future, not only molecular targeted drugs targeting cancer-related genes but also development of therapeutic methods targeting metabolism are expected as new cancer treatments.

Disclosure of potential conflicts of interest

The authors declare no potential conflicts of interest.

Acknowledgments

This study was supported in part by grants from the Japan Ministry of Education, Culture, Science and Technology (No.24592510, No.15K1079, No.17H01587 and No.19K09840), The Foundation of Osaka Cancer Research, The Ichiro Kanehara Foundation of the Promotion of Medical Science and Medical Care, The Foundation for the Promotion of Cancer Research, Kanzawa Medical Research Foundation, Shinshu Medical Foundation, and Takeda Foundation for Medical Science.

Author Contributions

T.H. performed most of the experiments and coordinated the project; T.H. conceived the study and wrote the manuscript. I.K. gave information on clinical medicine and oversaw the entire study.

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