Review Article

Ovarian cancer: new developments in clear cell carcinoma and hopes for targeted therapy

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Abstract

Until recently, ovarian clear cell carcinoma was recognized by its unique morphology and unfavorable patient outcome primarily due to tumor chemoresistance. Recently, specific molecular characteristics of ovarian clear cell carcinoma, such as PI3CA mutation, ARID1a mutation and MET amplification, have been elucidated. In addition, an association between endometriosis and the tumor has also been a focus of research in recent years. The aim of this review is to discuss the specificity and importance of molecular changes and various intriguing points that are not solved until today. Finally, future aspects, including hopes for the development of novel therapies, are discussed.

Key words: ovarian clear cell carcinoma, PI3CA mutation, ARID1A mutation, MET amplification, targeted therapy

Ovarian clear cell carcinoma: etiology and association with endometriosis

In the 1920s, Sampson (1) proposed that ovarian endometrial carcinoma develops from endometrial tissue. Clear cell carcinoma and endometrioid carcinomas are histological subtypes of ovarian cancer associated with endometriosis (2–6). Precancerous lesions, referred to as atypical endometriosis, have been identified in extraovarian and ovarian cancer cancers as atypical epithelium is continuous with the malignant tumor (7,8). However, the criteria for diagnosing atypical endometriosis was unclear given that the histological observance of atypical endometriotic cysts lining the epithelium were commonly observed with patchy erosion of the epithelial layer of the cyst wall with atypia. A single nucleotide polymorphism in the intron of ANRIL, a non-coding RNA that regulates p16 expression, was recently reported to be strongly associated with endometriosis (9) although p16 is expressed in endometriotic cysts (10) despite previous reports suggesting possible deletion of the CDKN2A/2B region in both endometriosis and related carcinomas as a result of iron-overload in the local environment (11). We did not find p16 deletion in clear cell carcinoma using array comparative genomic hybridization analysis (12), thus, atypical endometriosis and endometriosis-related ovarian

neoplasms may share several molecular alterations other than p16 deletion such as loss of PTEN expression due to mutation and loss of heterozygosity, ARID1A mutations, decreased hMLH1 expression due to epigenetic inactivation and HNF-1β up-regulation (10,13–15), suggesting a common molecular mechanism for lesion development. Oxidative stress causes direct effects, such as *in vitro* epithelial cell genome mutations (16). Furthermore, oxidative stress is considered to be the indirect underlying cause of tumorigenesis via stimulation of ectopic endometrial stromal cells to produce complement-associated factors, such as pentraxin 3, therefore exacerbating oxidative stress levels in the macrophage-rich environment (17).

Molecular pathogenesis of ovarian clear cell carcinoma

Recently, numerous genetic alterations involved in ovarian clear cell carcinoma have been revealed. First, the PI3CA gene was found to be specifically mutated in ovarian clear cell and endometrioid carcinoma samples, with a 33% frequency in clear cell carcinomas (18). Then, several studies using next-generation sequencing revealed that a significant proportion of clear cell carcinoma cases, ~50% in one

study and >50% in another study harbor a mutation of the ARID1A gene, which encodes a chromatin-remodeling complex protein (19,20). ARID1A mutation and the consequent loss of expression are frequently observed in ovarian clear cell carcinomas and endometrioid carcinomas of the ovary or endometrium (21). Recently, the precise molecular function of ARID1A as a tumor suppressor was elucidated; ARID1A regulates the transcription of p53-dependent genes, such as p21, by directly interacting with BRG1 and p53 (22). Loss of both ARID1A and PTEN promotes mouse ovarian carcinogenesis (23). KRAS mutations are present in a proportion of clear cell carcinomas (24) and activated K-Ras contributes to the growth of endometriotic lesions in an animal model (25). hMLH, a DNA mismatch repair gene, is another candidate involved in the malignant transformation of endometriosis (14,26). hMLH is the causal gene of Lynch syndrome, in which the risk of developing endometrial and ovarian cancers is significantly increased (27). Hypomethylation of long interspersed element-1 (LINE-1) is observed in both the clear cell and endometrioid carcinomas but not in atypical endometriosis, suggesting a role for this gene in tumorigenicity (28). Finally, we and others have found MET gene amplification in >20% of ovarian clear cell carcinoma cases (12,29). MET is a receptor tyrosine kinase; Ras/ERK and PI3CA-AKT-mTOR are the main downstream components (30). We also demonstrated that AKT2 is amplified in some cases (12) suggesting the importance of the pathway. However, a recent large study of >1000 patients focusing on MET amplification revealed that the highest frequency was noted in renal cancer and that MET amplification was only observed in 4% of ovarian cancers, all of which were serous carcinomas (31). A PI3CA mutation was also initially reported in all ovarian carcinomas regardless of histological subtype (32) whereas other reports demonstrated a significant presence in endometrioid or clear cell subtypes (18,33). Therefore, careful interpretation of histologic subtypes is required. Alternatively, because clear cell carcinomas are frequently observed in the Japanese populations (34) the molecular characteristics may differ from clear cell carcinomas in other Western countries. A comprehensive study to clarify this discrepancy and to elucidate the molecular progression from endometriosis development to carcinogenesis is needed. Furthermore, the diagnostic incidence among different countries using immunohistochemical analysis of clear cell carcinoma-specific proteins, such as HNF1-β (35) and napsin A (36) specific for clear cell carcinoma may also be useful to solve the enigma.

Targeted therapy for ovarian clear cell carcinoma: current information and future predictions

Ovarian clear cell carcinoma is associated with chemoresistance and a poor prognosis compared with serous or endometrioid carcinomas, especially in Asian cases (37–39). According to the international symposium of ovarian clear cell carcinoma, high-stage clear cell carcinoma cases exhibited the worst prognosis, whereas low-stage clear cell carcinoma patients exhibited a better prognosis than matched controls with high-grade serous carcinoma (40). Clear cell carcinoma with MET amplification exhibits an even worse prognosis (12,29). Thus, the establishment of alternative therapies for clear cell carcinoma, such as molecular targeted therapies, is urgently needed. It is difficult to target ARID1A given its tumor suppressive role related to p53 (22,23). MET is a good candidate given its high frequency and ovarian clear cell carcinoma-specific gene amplification (12,29). Whether PI3CA mutations and MET amplification are mutually exclusive is an important remaining question. Therapies targeting PI3CA, mTOR, vEGF and MEK1/2 are currently being examined clinically

or in animal models (41–45). Glypican 3 is a specific molecule expressed in ovarian clear cell carcinomas but not in normal tissues (46), and glypican 3 immunotherapies are being developed (47). NAC1 and its downstream fatty acid synthase is another proposed candidate for targeting clear cell carcinoma (48). CBX7 is a polycomb protein associated with ANRIL; we recently discovered that CBX7 expression is a marker of poor prognosis in ovarian clear cell carcinoma (49). Furthermore, CBX7 knockdown resulted in activation of the TRAIL pathway and clear cell carcinoma apoptosis, and we propose that TRAIL may serve as a good candidate for targeted therapy (49).

Conflict of interest statement

None declared.

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