Involvement of Rab25 Biomarker in Pathogenesis of Ovarian Cancer

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Abstract

Ovarian cancer is the third leading common gynecologic tumor and the leading cause of death in gynecological cancers worldwide and studies suggested that Rab25 is insinuated in the pathological process of ovarian cancer. Despite the availability of biomarkers for ovarian cancer detection, there are no specific markers that enable the early detection of ovarian cancers which open an avenue to Rab25 to be reviewed. A number of genes and proteins have been reported to be involved in the pathogenesis of ovarian cancers. Of them, Ras-related protein 25 (Rab25) is suggested to be linked to increased risk of ovarian cancer development. Rab25, an intracellular transport protein, belongs to the Rab small GTPase family and regulates various aspects of internalized membrane protein recycling and trafficking occurring inside the cells to the cell membrane. It is known to be involved in cell proliferation, and prevents apoptosis and invasion in ovarian cancer. Rab25 is highly found in epithelial cells and the expression of Rab25 proteins has been implicated to be ubiquitous. Upregulation of Rab25 has also been strongly shown to intensify the cancer cell proliferation and to prevent apoptosis in vitro and in vivo. Here in we will review the past and current studies implicating Rab 25 as potential biomarker in ovarian cancer in addition to pathogenesis This present study elucidate the role of Rab25 in pathogenesis of ovarian cancer its clinicopathological significance in addition to its potential as biomarkers in ovarian cancer.

Keywords: Rab25, Ovarian Cancer; Biomarkers.


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Introduction

According to epidemiological statistics in 2017 ovarian cancer (OC) was classified among the most prevalent gynecological malignancies and the leading cause of death among the entire women worldwide [1]. Annually worldwide reported to have an estimated number of 239,000 of newly diagnosed cases and mortality was reported to have 152,000 number of cases [2]. The maximum rates were seen in Eastern and Central Europe respectively. The average lifetime risk of developing OC is 1 in 75 and the mortality risk of 1 in 100 global ovarian population. The high incidence rate among ages standardized group was reported in developed countries including North America, Eastern and Central Europe with the rate over-reaching 8 per 100,000 with the intermediate rate seen in South America reach 5.8 per 100,000 with least rank in Asia and Africa [3]. Ovarian cancers are basically classified into three subdivisions: epithelial ovarian carcinoma, sex cord stromal, and germ cell tumors on the basis of the histogenesis and direction of their differentiation. Meanwhile, each of these three types also includes a series of subtypes. Carcinoma of ovarian tissues is labelled by giving coded C56 by the International Classification of Diseases and Related Health Problems 10th revision code (ICD-10), and considered as a disease of heterogeneous group, which included primary invasive epithelial, borderline epithelial and non-epithelial ovarian neoplasm. [3] ‘Invasive epithelial’ OCs have established root based on molecular genetics and distinctive morphological features and can extensively be classified into two groups [4]. Type I are slowly growing tumors with effective prognosis, such as low grade serous, low-grade endometroid, clear cell, mucinous and transitional (Brenner) carcinomas. These tumors have lack of gene mutations of TP53 with each histologic type which manifest clearly in molecular genetic profile. These carcinomas have similar lineage that corresponding to benign cystic neoplasms, often through an intermediate (borderline tumors) which supporting the morphologic constancy of tumor progression. Endometrioid and clear cell tumors are associated with endometriosis [5] and consider the endometrium to be the originality of these ovarian neoplasms [6]. Mucinous and transitional (Brenner) tumors originate from the fallopian tube of –mesothelial junction by a process of metaplasia [4]. Ultrasound screening appears cancer (STIC) lesions in the fimbriae end of the fallopian tube , epithelial ovarian cancers account for about 80% of all ovarian cancers, including serous tumor, mucinous tumor, endometrioid tumor, clear cell tumor, and transitional cell tumor. A number of genes and proteins have been reported to be involved in the pathogenesis of ovarian cancers. Of them, Ras-related protein 25 (Rab25) is suggested to be linked to the increased risk of ovarian cancer development [6]. It is known that Rab25 is involved in promoting cell proliferation, and preventing apoptosis and invasion in the ovarian cancer and imbalance of Rab gene expression, especially Rab25, may induce the aggressiveness of human cancers, as observed in the ovarian and breast cancers, which is associated with the increased Rab 25 mRNA levels [7]. However, the molecular mechanism by which Rab25 mediates its functions remains idiopathic.

Studies have showed that Rab25 is implicated in the pathological process of ovarian cancer and each forms of ovarian cancer are detectable at various stages of their formation [8, 9]. Rab 25 play a significant role in the regulation of the neoplastic transition. Rab25 is highly found in epithelial cells and the expression of Rab25 proteins has been implicated to be ubiquitous [10]. The overexpression or loss of Rab25 expression in malignancies suggests that disordered or reordered intracellular communication is a characteristic of the transformation process [11, 12]. Rab25 is dominantly expressed on human mammary epithelial cells and the role of Rab25 in the cancers clearly shows that it is involved in epithelial cell intracellular transformation [13]. Few studies have investigated the expression of Rab25 in patients with epithelial ovarian cancers [6, 9, 13]. Although some studies suggested that Rab25 mRNA is highly expressed in the ovarian cancers, detailed clinical studies in Rab25 protein level are limited [14]. So far, only few studies have investigated the expression of Rab25 in patients with epithelial ovarian cancers [6, 9]. A very limited number of clinical studies (conducted by Schlech, L. et al, 2009, Schwartz, S.L., et al, 2007) have reported the distribution of Rab25 expression in the different classes of ovarian cancers where their studies strongly showed that Rab25 protein is highly expressed in epithelial ovarian tumor, including serous, mucinous, endometrioid and clear cells [9, 15]. Similar results was also reported by Zhao.M et al in another study [16].

Overview on Rab 25 and Ovarian Cancer

Ovarian cancers are subdivided into three subtypes; epithelial ovarian cancer, sex cord stromal ovarian tumors, and germ cell tumors based on histology origin. In addition, the predominantly subtype is epithelial ovarian cancers which account for about 80% of all ovarian cancers include serous tumor, mucinous tumor, endometrioid tumor, clear cell tumor, and transitional cell tumor (Brenner’s tumor). The germ cell tumors account for about 15–20% of all ovarian cancers while the most dominant germ cells tumor subtypes are dysgerminoma and yolk sac tumors respectively. A less common but significant subtype is ovarian teratoma. The most common sex cord stromal cancer which accounts for about 5–10% of all ovarian cancers is granulosa cell cancer. Each of these forms of ovarian cancer is detectable at various stages of their formation by various tumor markers, one potential biomarker is Rab25 which is a family member of Rab protein. Currently, 70 human Rab proteins identified [17, 18] made up the largest branch of Ras superfamily [19]. Rab25 is involved in multifactorial cellular functions, including cell proliferations, cell mobility, cellular trafficking, protein transport and signal transduction [20, 21]. Rab25 also regulates apical transport and recycles of vesicles to the plasma membrane [22, 23] and involved in tumor formation and progression. The fundamental role of Rab25 in the cancers is cancer cell type dependent, in view of the fact that it has been indicated to be tumor oncogene or tumor suppressor. Its functions depends on its potentiality to influence chloride Intracellular channel protein 3 (CLIC3), which includes alpha 5 beta 1 integrins [24]. It is indicated that in the presence of CLIC3, Rab25 acts as oncogene, whereas in the absence it acts as tumor suppressor gene. When Rab25 acts as oncogene it boosts alpha 5 beta 1 integrins recycling to the plasma membrane to enhance the ovarian cancer progression. Through its direct binding Rab25 inhibit the apoptotic cellular mechanism and autophagic...
cell death. Up regulation of Rab25 shown to decreased Ultra Violet light (UV) which induced apoptosis in ovarian tumors and impediment of Rab25 was appeared to increase apoptosis in ovarian tumor cells. Also its expression is highly pronounced around 80% of ovarian tumors samples in a comparison to normal ovarian epithelium, and remarkably increased in Rab25 expression link with increasing tumor stage [25].

Role of Rab 25 in Ovarian Cancer Treatments and its Prognostic Significance

The fundamental treatments of ovarian cancer depend on the subtypes of ovarian cancer and its surgical staging in order to achieve maximum therapeutic efficacy. In epithelial type of ovarian tumors, patients categorized in early staging which includes stage Ia or Ib with grade 1 or 2 a total hysterectomy and bilateral salpingoophorectomy should be performed without chemotherapy. Patients with stage Ia or IB, with grade 3 and all stage IC and stage II, tumors were cured with single or combined chemotherapy includes cisplatin and paclitaxel. In advanced stage III-IV, surgical cytoreductive was primarily performed with the aim of removed all gross diseases and was followed by six courses of platinum-based chemotherapy including cisplatin [17, 20]. Rab25 protein expression in ovarian tumors shown to have clinical significance in prognosis of the diseases, different studies done to proof this relevant statement. Cheng KW et al reported that overexpression of Rab25 was more linked to advanced stages of ovarian cancer with poor survival outcome [26]. But this result was against the study done by Sheach LA et al which was found that overexpression of Rab 25 protein had no interaction with the advanced stages of epithelial ovarian cancer, however there is limitation their study due to the small sample size of the population enrolled in the study [27]. Yet a recent study with the large number of sample size shown that overexpression of Rab 25 was not interconnected with advanced stages of epithelial cancer. This implied that in both small and large sample population there were no correlation between the Rab25 overexpression with clinical advanced stage of epithelial ovarian cancer. Up regulation of Rab25 have shown to shorten the diseases free period and increase the aggressiveness of ovarian cancer [26]. Patients with Rab25 overexpression have the tendency to display a significant resistance to cisplatin which made second and third line to be more effective [27, 28]. Temel, S G et al 2020 report that Rab25 suppresses chemotherapy-induced mitochondrial apoptosis signaling in ovarian cancer cell lines and primary ovarian cancer cells. Whereby RAB25 blocks chemotherapy-induced apoptosis upstream of mitochondrial outer membrane permeabilization by either increasing antiapoptotic BCL-2 proteins or decreasing proapoptotic BCL-2 proteins. In particular, BAX expression negatively correlates with RAB25 expression in ovarian cancer cells and suppressing RAB25 by means of RNAi or RFP14 inhibitory hydrocarbon-stapled peptide sensitizes ovarian cancer cells to chemotherapy as well as RAB25-mediated proliferation, invasion and migration suggesting that RAB25 is a potential therapeutic target for ovarian cancer [29].

Rab25 and ovarian cancer metastasis

Ovarian cancer is a dangerous malignant disease due to its quick and early metastasis. Their primarily metastasis way is by direct exfoliation called transcroclemic dissemination, the sites of metastasis usually follow the circulatory pathway of the peritoneal fluid. This rapid spread is exacerbated by ascitic fluid which embeds the primary tumor and acts as a media in order to promote dissemination to the peritoneum and the omentum respectively. Intraperitoneal dissemination spread is an early event to appear and makes the reasons why these tumors are seldom or barely detected in early stages. In advanced diseases, intraperitoneal tumor spread result on accumulation of ascites in the abdomen and intermittent bowel obstruction known as carcinomatous ileus which manifest condition like malnutrition, cachexia and even death. Lymphatic spread can be another common way of ovarian cancer spread along the retroperitoneal pelvic and para aortic lymph nodes. Hematological spread is liable for distant metastases to the lungs and brain. Ectopic expression of Rab25 accelerate Epithelial Mesenchymal Transition (EMT) cascade which is potent component in metastatic pathway in ovarian cancer cells by modulating E-cadherin and Snail protein Expression [26]. Caswell et al have shown that Rab 25 is connected with alpha 5beta 1 integrin by stimulate metastasis through alteration of membrane trafficking protein and assist localization of the vesicle at the cell [26].

Pathophysiology of Ovarian Cancer

The initial event in the occurrence of Ovarian cancer begins when there is abnormal ovarian cell growth occur. Cancer originates when new cells form unrequired, and old or damaged cells do not undergo apoptosis as in normal cell as a resulting buildup of extra cells often forms a mass of tissue called a growth or tumor. These abnormal cancer cells have many genetic abnormalities that cause them to grow excessively [31]. When an ovary release the ovule this will bursts and changed to the corpus luteum. Repeated event of ovulation for a long time initiate repair mechanism of the ovary by dividing cells, which can lead to mutations in each division [32]. It has been reported that the common gene mutations in ovarian cancer occur in NFI, BRCA1, BRCA2, and CDK12. Furthermore Type I ovarian cancers, is characterized as less aggressive, and tend to have microsatellite instability in different genes, including both oncogenes most notably (BRAF and KRAS) and tumor suppressors (PTEN) [33]. The commonest gene mutations in type I cancers are KRAS, BRAF, EBBB2, PTEN, PIK3CA, and ARID1A [32]. Type I cancers tend to develop from precursor lesions, meanwhile the type II cancers, is the more aggressive type and have several genes mutated, including p53, BRCA1, and BRCA2 [33]. Type II cancers can develop from a serious tubal intraepithelial carcinoma and in those have p53 mutations, the loss of both functional genes is require for cancer to develop [32]. In 50% of high-grade serous cancers which shown that, homologous recombination DNA repair is dysfunctional, as are the notch and FOXM1 signaling pathways with almost always have p53 mutations. Apart from this, mutations in high-grade serous carcinoma are difficult to characterize beyond their high degree of genomic instability behavior. BRCA1 and BRCA2 are fundamental role in homologous recombination DNA repair, and germline mutations these genes are found in approximately 15% of population with ovarian cancer [34].
The key common mutations in BRCA1 and BRCA2 are the framework of mutations that emerged in a small founding population of Ashkenazi Jews [32]. It is uncommon for mucinous carcinomas to have mutations in KRAS and amplifications of ERBB2 (Her2/neu) and it accounts for 100% [33]. Generally, its account 20% of ovarian cancers have mutations in Her2/neu [34]. Serous carcinomas may develop from serous tubal intraepithelial carcinoma, rather than developing voluntarily from ovarian tissue. Several types of ovarian carcinomas develop from cortical inclusion cysts, which are groups of epithelial ovarian cells inside the stroma [35]. Besides, the genetic role in the pathogenesis of ovarian tumor, the role of the immune system and the tumor microenvironment are also established. The cytotoxic T cell infiltration in ovarian tumors corresponds with the improvement in overall survival, as shown by several group [35, 36].

Another component in key role of pathogenesis of ovarian tumor is the tumor microenvironment like angiogenesis which show a crucial role in the pathogenesis of epithelial ovarian cancer, by promoting tumor growth [37, 38]. Vascular endothelial growth factor (VEGF) is one of the most potent pro-angiogenic factors identified in ovarian cancer, while other pro-angiogenic factors that identified, including fibroblast growth factor, angiopoietins, endothelin, IL-6, IL-8, macrophage chemotactic proteins and platelet-derived growth factors [39]. Recent studies suggest that pelvic inflammatory disease may slightly increase risk of serous ovarian cancer [40, 41, 42] and genital powder use may increase risk of all ovarian cancer histotypes [43] while high prediagnostic C Reactive Protein (CRP) levels have also been associated with increased risk [44], lending support to the hypothesis that inflammation contributes to ovarian carcinogenesis [45].

Routine Biomarkers for Diagnosis of Ovarian Cancer

Early diagnosis of ovarian cancer is the potential feature on improving the 5-year survival rate of the patients. The standards diagnostic methods for OC includes the history of underlying diseases, physical examination, index diagnosis symptoms; imaging and histological diagnosis.

To confirm the diagnosis of ovarian cancer a tissue biopsy must be performed. Screening is an implementation of a single test or multiple tests conducted to an asymptomatic individual who is at risk, in order to detect the presence of underlying diseases at an earlier stage in order to provide accurate management on time. Among biomarkers (Table 1) serum CA-125 is an ideal tumor marker on detection of ovarian cancer and found marked to be elevated [40]. Suh et al, 2010 reported that there is markedly increase of CA-125 level in the serum, which is the key marker for ovarian cancer. Normal value of CA-125 is below 35 IU/ml. Meanwhile neither of the increased level of CA-125 have suggested that women have ovarian tumor however some conditions including endometriosis may mimic the same outcome (Bankhead et al, 2007). Elevation of serum CA-125 level has been estimated in 80% of patients with advanced ovarian cancer with 50%-60% elevated in early stage OC. Single detection results in false positive outcome because increase CA-125 also implicated in gynecological malignancy conditions such as bladder, breast, cervical, lung, liver [47] non-gynecological condition such diverticulitis [48] and in a normal physiological condition including menstruation and pregnancy noted to be elevated [49]. Currently the diagnostic biomarker used in OC to determine its recurrence and prognosis tendency are CA-125 levels even though has a limitation with poor specificity and less than 60% sensitivity [50].

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<td>Epithelial ovarian cancer</td>
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<td>Endodermal sinus tumor</td>
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Rab25 a Potential Biomarker in Ovarian Cancer

Studies revealed that tumor cells overexpressing the protein Rab25 are more aggressive and are associated with poorer prognosis therefore in this perceptive Rab25 may serve as a therapeutic target or key biomarker in tumor events. Breast and ovary tumors studies in comparison to the disease prognosis revealed that decrease level of Rab25 protein was associated with a better prognosis in both tumors respectively. Furthermore to support those findings, patients with early stage (I and II) ovarian cancer who had a decrease Rab25 protein level expression had an 80% survival in five years after treatment, in contrast to 50% survival in a highly expressed Rab 25. Additionally, women with advanced breast tumor, a low level of Rab25 protein expression was related with a 60% five-year survival, in a correlation with 40% if Rab25 protein expression was increased respectively. This result obtained open the light in research field by adding other known protein molecular markers in disease progression and contribute to a remarkable role in predicts the outcome in breast or ovarian cancer. The main function of Rab25 is to activate the PI3 kinase/AKT/PTEN protein pathway which play a significant role in cell growth and survival respectively. This pathway, explicit in various tumor suppressor genes and oncogenes and is targeted by genetic mutations in so many cancers more often than any other signaling pathway. Reported from the laboratory study conducted in both in vitro and in vivo using human breast and ovarian tumor xerographs in mice, shown that either upregulation or downregulation of Rab25 modify tumor growth. Marked increase of Rab25 was linked with poor prognosis and hence play a tumorigenic role in tumor progress observed in ovarian cancer [51, 52, 53]. Up to date studies have shown connection between Rab GTPase dysfunction and related regulatory proteins in human diseases, including cancer [54, 55, 56].

Conclusion

In brief Rab25 is strongly implicated in the pathogenesis of ovarian cancer. However few studies have been conducted regarding Rab25 and its clinical significance in ovarian cancer as well as its distribution in different subtype of ovarian. Therefore it should interesting to investigate in deep this potential biomarker in ovarian cancer. This contribution will be of key value in evaluation of Rab25 as potential biomarker in ovarian cancer

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Conflict of Interest Statement
All authors declare no conflict of interests.

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