Subtype specific biomarkers associated with chemoresistance in epithelial ovarian cancer

Abhilash Deo¹,²,#, Souvik Mukherjee¹,²,#, Bharat Rekhi²,³, Pritha Ray¹,²

¹Imaging Cell Signalling and Therapeutics Lab, Advanced Centre for Treatment, Research and Education in Cancer, Tata Memorial Centre, Navi Mumbai, ²Homi Bhabha National Institute, Anushakti Nagar, ³Tata Memorial Hospital, Dr. E Borges Road, Parel, Mumbai, Maharashtra, India

*These authors equally contributed to the review

Address for correspondence:
Dr. Pritha Ray, Imaging Cell Signalling and Therapeutics Lab, KS-338A, ACTREC, Tata Memorial Centre, Kharghar, Navi Mumbai - 410 210, Maharashtra, India. E-mail: pray@actrec.gov.in

ABSTRACT

In spite of the advent of many high throughput technologies, tumor tissue biomarkers are still the gold standard for diagnosis and prognosis of different malignancies including epithelial ovarian cancer (EOC). EOC is a heterogeneous disease comprised of five major subtypes which show distinct clinicopathological features and therapy response. Acquirement of chemoresistance toward therapy is a major challenge for successful treatment outcome in EOC patients. Several markers have been tested by immunohistochemical method to evaluate their prognostic merit to predict clinical outcome. However, a vast majority of such markers have been assessed for high-grade serous and clear cell ovarian cancer, among all subtypes of EOC. The current review elaborates upon those biomarkers that can potentially predict chemoresistance with subtype specificity.

KEY WORDS: Biomarkers, chemoresistance, epithelial ovarian cancer

INTRODUCTION

Despite recent advances in chemotherapeutics and vast research elucidating mechanisms of resistance, ovarian cancer (OC) still remains the third leading cause of cancer-related deaths in India and eighth worldwide among women.¹ Epithelial ovarian cancer (EOC), which is the most common type of OC, has a 5-year overall survival (OS) rate of 30%–50% cumulative for all stages.² EOC is further classified into five major histotypes as high-grade serous, low-grade serous, mucinous, endometrioid, and clear cell carcinoma that possess distinct molecular, genetic, and immunohistochemical features with differential clinical course.³,⁴,⁵ Chemotherapy regimen for each subtype involves the use of multiple drugs in different combinations that have been explored to achieve optimal clinical response (CR) and overall survival (OS).³ However, the majority of patients succumb to the disease, an outcome resulting to a large extent from increasing resistance to chemotherapy.⁶ Therefore, intrinsic or acquired chemoresistance is the primary impediment that imposes a great challenge to therapy response in EOC patients leading to their dismal survival outcome. Therapy associated chemoresistance is usually monitored through radiological assessment (RECIST/PERCIST criteria) in clinics.⁷,⁸ However, tissue-specific biomarkers that can offer predictive assessment are equally important and may generate cues for therapeutic approaches for chemoresistant or relapsed tumors. Since second line chemotherapy but not the second surgery is commonly recommended for treating chemoresistant EOC tumors, evaluation of biomarkers in relapse biopsies is rare. As a result, majority of such studies have been carried out in tumor samples procured during upfront or intraoperative surgery post neoadjuvant chemotherapy (NACT). A myriad of biomarkers has been evaluated for their prognostic merit in EOC, which includes receptor tyrosine kinases (EGFR, IGF1R), apoptotic proteins (p53, cell-cycle kinases), angiogenic factors (VEGF, EphA2), and immune mediators (Immunoglobulins, B7-H3) to list a few. Moreover, genetic and epigenetic markers are also being explored.⁹ The aim of this short review is to comprehensively discuss tissue-based tumor biomarkers that can predict chemoresistance in different subtypes of epithelial ovarian cancer. Only those reports that have shown direct association of biomarker with chemoresistance, relapse, or progression-free survival (PFS) have been included in this review. Unfortunately, apart from high-grade serous and clear
cell carcinoma, there is no report for other subtypes that have highlighted any biomarker with a merit to predict chemoresistance and requires substantial exploration.

HIGH-GRADE SEROUS OVARIAN CARCINOMA (HGSOC)

HGSOC is the most prevalent form among EOC subtypes that accounts for almost 70% of SOC cases and has the worst survival rate across all subtypes of EOC. These tumors arise from tubal or ovarian surface epithelium. While TP53 mutation is found in nearly 80% of the cases, high Ki67 proliferative index (50%–75%) is a common feature. HGSOC tumors are highly genetically unstable with frequent chromosomal rearrangements. Moreover, mutant BRCA 1/2 signature is associated in around 90% of hereditary cases. For HGSOC patients, clinical management proceeds with cisplatin and paclitaxel based NACT followed by subsequent radical resection of the tumor. HGSOC patients initially respond better to the first-line therapy; however, in 70% of the cases, there is a relapse within 2 years from the start of treatment because of acquired chemoresistance. Therefore, although complete response (CR) is achieved in more than 70% of the cases, development of resistance ultimately results into recurrent disease in the majority of the cases. For HGSOC, a significant number of biomarkers were studied to investigate their association with disease-free survival, overall survival, and recurrence due to chemoresistance. Biomarkers that had been evaluated by immunohistochemistry and were reported to be associated with OS and PFS and recurrence are discussed in the following sections.

THE MITOTIC ARREST DEFICIENCY PROTEIN 2 (MAD2)

MAD2 is a central component of spindle assembly checkpoint and its implications in drug resistance have been extensively studied in cell lines. In the study by Furlong et al., immunohistochemical score of MAD2 protein was correlated with PFS of 82 HGSOC intraoperative tumor samples by cox regression analysis. Low intensity of nuclear MAD2 was found to predict poor PFS in these patients with a hazard ratio of 4.689. Interestingly, this study also shows coexistence of MAD2 positive and negative cells in the same tissue specimen. This apparent heterogeneity in the MAD2 expression within tumor tissue may indicate the resistant potential of OC cells that might eventually lead to recurrence of the disease.

CHECK POINT KINASE 2 (CHK2)

Chk2 is a central key protein that mediates response to genotoxic stress. For HGSOC patients, activation of Chk2 has been shown to render sensitivity to platinum-based therapy. In this study, an advanced stage HGSOC cohort having residual disease >2 cm was subdivided into platinum responders and non-responders, wherein the immunoreactive score of Chk2 was correlated with the therapy response. Logistic regression analysis showed that high Chk2 expression predicts good response to platinum-based chemotherapy with odd ratio of 0.132.

INSULIN-LIKE GROWTH FACTOR 1 RECEPTOR (IGF1R)

IGF1R is a tyrosine kinase commonly found to be overexpressed in HGSOC. In an exploratory study, our group has prospectively evaluated the prognostic nature of IGF1R levels in a small cohort of 19 patients. Longitudinal assessment from paired chemonaive (ascites derived cells) and post NACT (intraoperative) primary and metastatic tumor samples revealed a significant increase in IGF1R transcript expression post NACT. Our data unveiled that the patients with higher IGF1R expression (more than or equal to median) had prolonged OS (median not reached) and DFS (26.7 months) compared to the ones with lower IGF1R expression (less than median) (OS: 27.5 months; DFS: 11.9 months) at transcript level [Figure 1a and b]. This finding was further confirmed at protein level through immunohistochemical analyses [Figure 1c]. Intriguingly, bivariate analysis also showed a significant positive correlation between IGF1R and hCTR1 at transcript as well as protein level in chemo-treated samples [Figure 1d and e]. hCTR1 is a high affinity copper uptake protein responsible for cisplatin uptake and thus indicates treatment efficiency. Therefore, the positive correlation between IGF1R and hCTR1 might explain the prognostic nature of IGF1R. Although the clinical end point of the study was DFS rather than PFS, the good prognostic nature of IGF1R and its association with hCTR1 makes it a potential biomarker to predict chemoresistance in these patients. However, a larger cohort study with cisplatin-resistant cases is warranted.

PROSTAGLANDIN D2 (PGD2)

Prostaglandins are lipid-based arachidonic acid derivatives that regulate follicle-stimulating hormone (FSH)-mediated proliferation, differentiation, and steroidogenic activity in normal ovary. In the study conducted by Alves et al., high expression of PGD2 has been positively correlated with DFS, absence of relapse, and sensitivity to platinum-based therapy. This study has also established PGD2 as an independent prognostic marker associated with relapse with a hazard ratio of 0.37 as determined by multiple cox regression analysis.

ERCC1

ERCC1 is one of the key components of nucleotide excision pathway. Scurry et al. have shown that ERCC1 levels significantly increase post NACT in HGSOC patients. The mean OS for the patients showing high ERCC1 levels (neoadjuvant group) shows significantly longer survival (141.6 months) than those with low ERCC1 levels (61 months). In conclusion, ERCC1 can act as a potential biomarker that can predict platinum response and OS in HGSOC patients undergoing NACT. However, in chemo naive tumors, no such correlation was observed.
NOTCH3

Notch 3, a bona fide oncogene, is altered in approximately 20% of HGSOC patients, has a definite role in both acquisition of chemoresistance and disease progression. In two separate studies, it has been identified as a significant prognostic factor in patients with relapsed tumor. In the study, carried out by Jung et al., the authors have followed up 25 patients harboring serous carcinomas with mean follow-up duration of 32 months (ranging from 9 months to 86 months). Out of all, nine cases (36%) clinically displayed recurrent/persistent tumor with acquired chemoresistance toward first-line chemotherapeutic intervention comprising of cisplatin and paclitaxel. The total cohort (including 5 subjects deceased during follow-up) were divided into two: the higher-expressing group \((n = 12)\) and the lower-expressing group \((n = 13)\), with respect to the cut-off value of 2-fold in Notch 3 expression compared to that in the benign counterpart. Higher expression of Notch 3 (>2 fold) was associated more significantly with chemoresistant serous carcinomas relative to the low-expressing group (58.3% vs 15.4%), which is suggestive toward the role of Notch 3 as a possibly valuable predictive marker for chemoresistance. The Rahman et al. group had highlighted the possible association of Notch3 and stage III/IV of ovarian adenocarcinoma with respect to progression-free survival. Albeit there is no direct correlation of Notch3 in the development of chemoresistance, 3 patients with relapse had Notch3 overexpression out 5 recurrent cases, which led to poorer progression-free survival.

OVARIAN CLEAR CELL CARCINOMA (OCCC)

Although rarer in Western population (5% of all cases), clear cell carcinoma is one of the most poorly prognosticated subtypes of EOC. Notably, it has a higher incidence rate in South Asian population with the highest figures registered in Japan (20% to 25% of overall EOC cases). It is a distinct subtype characterized and differentiated from serous adenocarcinoma and hobnail cell borderline tumor by the overexpression of napsin A, an aspartic proteinase which bears a critical diagnostic value in OCCC. The tumor has intrinsic resistance toward therapy ending up
with 22%–56% patients responding to platinum-taxol in case of detection at stage III and onwards. There have been several studies and histopathological protocols which have tried to define the clear cell tumor in terms of resistance and prognosis. Here, we discuss several markers that have been looked into across many studies to assess the acquisition of chemoresistance.

The expression of eight genes, including napsin A, were demonstrated to be upregulated in OCCC specimens. They are X-linked inhibitor of apoptosis, E3 ubiquitin protein ligase, napsin A aspartic peptidase (NAPSA), protein phosphatase 2 regulatory subunit 13 like, glypican 3, ATP-binding cassette, sub-family F, member 2, glutathione peroxidase 3, annexin A4 and aldehyde dehydrogenase 1 family, member A1 (ALDH1A1). Among these eight genes, NAPSA, GPX3, and ALDH1A1 were markedly overexpressed and may be possible novel biomarker candidates. However, napsin A does not play much role in prognosis of chemoresistance in OCCC per se albeit its association with high-grade morphology or Met amplification leading to bad prognosis had been reported. This majorly happens to be misdiagnosed cases of serous adenocarcinoma than true OCCC.[37]

**GLYPCAN-3**

Glypcan-3 (GPC3), a cell-surface heparan sulfate proteoglycan, binds to the cell membrane via glycosylphosphatidylinositol anchors and its product is believed to regulate cellular growth and apoptosis by interacting with a variety of morphogenic or growth factors, such as Wnt, fibroblast growth factor 2, and bone morphogenic protein 7 in a tissue-specific manner. For the clarification of the significance of glypcan-3 expression in ovarian clear cell adenocarcinoma, it was evaluated by immunohistochemistry in non-neoplastic as well as neoplastic ovaries, and remaining Müllerian duct derivatives including endometrium in different menstrual phases. Among the examined benign lesions, glypcan-3 expression was identified exclusively in the endometrial epithelium in the gestational period. A total of 213 cases of ovarian adenocarcinoma, including 94 clear cell adenocarcinomas, were studied. Glypcan-3 expression was observed in 44% of clear cell adenocarcinomas, whereas it was rarely observed in other histological subtypes: mucinous (4%), endometrioid (5%), and serous (11%). In cases of clear cell adenocarcinoma, there was correlation between glypcan-3 expression and clinicopathological aspects, such as tumor stage, lymph node metastasis, peritoneal dissemination, and death rate although glypcan-3 expression was significantly associated with poor overall survival in stage III/IV clear cell adenocarcinoma cases. The results suggest that overexpression of glypcan-3 can possibly be associated to the development and aggressive behavior of ovarian clear cell adenocarcinoma.[40]

**ALDEHYDE DEHYDROGENASE (ALDH1A1)**

ALDH1A1 is a catalase that oxidizes aldehyde-containing molecules and ALDH, therefore, plays an important role in cellular homeostasis. In cancer cells, it assists in both energy production (through retinoic acid synthesis) and also in deactivation of drug molecules (by action on the aldehyde group).[41] Many studies have associated it with tumor initiating potential of cells and poor prognosis of the disease. A study by Kuroda et al. is the first one to report that along with serous adenocarcinoma, ovarian clear cell carcinoma can also be prognosticated poorly on the basis of high ALDH1A1 expression in immunohistochemistry.[42]

Other than these biomarkers, there are several other putative proteins that are highlighted in other cohort studies.

**HOMEBOX A10 (HOXA10)**

HOXA10 is a homeobox allotype gene in HOX family.[43] In a single center study by Li et al. at Fudan Hospital, China, 29°CCC patients were evaluated for HOXA10 expression and correlated with survival. HOXA10 expression was negatively correlated with the 5-year survival rate (R = -0.442). The 5-year survival rate was only 30% in the 20°CCC patients with positive HOXA10 expression although the 5-year survival rate was 55.6% in the 9 patients who did not have HOXA10 expression as determined by Kaplan–Meier analysis.[44]

**ARID1A**

BAF250a, the protein encoded by ARID1A [the AT-rich interactive domain 1A (SWI-like) gene], is one of the accessory subunits of the SWI–SNF complex chromatin remodeling complex which modulates the repression/de-repression of several promoters. It acts as a tumor suppressor by nature in OCCC as suggested by the mutation pattern. ARID1A loss has been correlated with shorter progression-free survival (PFS) in patients with clear cell carcinomas treated with platinum-based chemotherapy. Loss of ARID1A expression tended to correlate with shorter overall survival in patients with ovarian clear cell carcinomas treated with platinum-based chemotherapy.[46] In addition, ARID1A mutation can be associated with higher stages of FIGO classification and augmented CA125 level.[47]

**HNF-1B**

Hepatocyte nuclear factor-1β (HNF-1β), on the other hand, imparts therapy resistance chemoresistance due to its ability to reduce ROS generation and increased Warburg effect.[48] Extensive nuclear localization of HNF-1β is reported in OCCC. In two separate large cohort studies—one in Australian population known as Australian ovarian cancer patients (AOCS) and another in Japanese population called as high-volume Japanese university clinical network (JIKEI)—HNF1B loss (absence of nuclear staining) has been attributed to longer PFS and OS.[49]

Table 1 summarizes all the markers discussed in this review.

**CONCLUSION**

In conclusion, clear understanding of subtype specificity and underlying clinical behavior is a key to design therapeutic strategy
Deo, et al.: Biomarkers of chemoresistance in ovarian cancer subtypes

Table 1: Summary of biomarkers associated with chemoresistance for high-grade serous and clear cell ovarian cancer

| Biomarker   | Subtype (EOC) | Status in chemoresistance | References |
|-------------|---------------|---------------------------|------------|
| MAD2        | HGSOC         | Low expression            | [22]       |
| Chk2        | HGSOC         | Low expression            | [24]       |
| IGF1R       | HGSOC         | Low expression            | [26]       |
| Prostaglandin | HGSOC      | Low expression            | [28]       |
| ERCC1       | HGSOC         | Low expression            | [29]       |
| Notch3      | HGSOC         | Overexpression            | [32,33]    |
| Glypican 3  | OCCC          | Overexpression            | [38-40]    |
| ALDH1A1     | OCCC          | Overexpression            | [41,42]    |
| HomeoboxA10 | OCCC          | Low expression            | [43,44]    |
| ARID1A      | OCCC          | Loss of function          | [45-47]    |
| HNF-1β      | OCCC          | Overexpression            | [48,49]    |

For optimal response. Currently, radiological examination is the gold standard for the assessment of therapy response and tumor relapse. However, differential clinical behavior and development of chemoresistance act as confounding factors in predicting survival outcome solely on the basis of radiological findings. Therefore, subtype specific biomarkers discussed in this review may significantly contribute to better disease management in recurrent cases. Chk2, PGD2, and NOTCH 3 are promising biomarkers as their merit has been clearly demonstrated for the prediction of chemoresistance in HGSOC patients. For MAD2, IGF1R, and ERCC1, however, cohort studies with larger sample size and appropriate end points are warranted to validate their potential. Whereas in OCCC, glypican-3 and ALDH1A1 are already established biomarkers to predict chemoresistance. In addition, HOXA10, HNF-1β, and ARID1A can be putative biomarkers with potential to prognosticate the response to therapy upon relapse. Evaluation of more biomarkers and in other subtypes of EOC are warranted in future to predict/evaluate appropriate therapy in personalized way.

Acknowledgements
Department of Biotechnology (BT/PR141/MED/30/680/2011 and BT/PR27126/Med/30/1943/2017) for funding to PR and ACTREC–TMC for fellowship to AD and SM.

Financial support and sponsorship
Department of Biotechnology and ACTREC–TMC.

Conflicts of interest
The authors do not have any conflict to declare.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424.
2. Saini SK, Srivastava S, Singh Y, Dixit AK, Prasad SN. Epidemiology of epithelial ovarian cancer, a single institution-based study in India. Clin Cancer Investig J 2016;5:20-4.
3. Chen VW, Ruiz B, Killeen JL, Coté TR, Wu XC, Correa CN. Pathology and classification of ovarian tumors. Cancer 2003;97:2631-42.
4. Kurman RJ, Shih IM. The origin and pathogenesis of epithelial ovarian cancer–a proposed unifying theory. Am J Surg Pathol 2010;34:433-43.
5. Piver MS. Treatment of ovarian cancer at the crossroads: 50 years after single-agent melphalan chemotherapy. Oncology (Williston Park) 2006;20:1156, 1158.
6. Davidson B. Biomarkers of drug resistance in ovarian cancer—an update. Expert Rev Mol Diagn 2019;19:469-76.
7. Eisenhauer E. Optimal assessment of response in ovarian cancer. Ann Oncol 2011;22:viii49-51.
8. Wahl RL, Jacene H, Kasamon Y, Lodge MA. From RECIST to PERCIST: Evolving considerations for PET response criteria in solid tumors. J Nucl Med 2009;50:1225.
9. Huang J, Hu W, Sood AK. Prognostic biomarkers in ovarian cancer. Cancer Biomark 2011;8:231-51.
10. Kim J, Park EY, Kim O, Schilder JM, Coffey DM, Cho CH, et al. Cell origins of high-grade serous ovarian cancer. Cancers (Basel) 2018;10:433.
11. Ahmed AA, Etemadmoghadam D, Temple J, Lynch AG, Riad M, Sharma R, et al. Driver mutations in TP53 are ubiquitous in high grade serous carcinoma of the ovary. J Pathol 2010;221:49-56.
12. Christie M, Oehler MK. Molecular pathology of epithelial ovarian cancer. J Br Menopause Soc 2006;12:57-63.
13. Mendiola M, Redondo A, Heredia‑Soto V, Herranz J, Berjón A, Hernández A, et al. Predicting response to standard first-line treatment in high grade serous carcinoma by angiogenesis‑related genes. Anticancer Res 2018;38:5393-400.
14. Lisio MA, Fu L, Goyeneche A, Gao ZH, Tellera C. High‑grade serous ovarian cancer: Basic sciences, clinical and therapeutic standpoints. Int J Mol Sci 2019;20. pii: E952. doi: 10.3390/ijms2004952.
15. Matsulonis UA, Sood AK, Fallowfield L, Howitt BE, Sehouli J, Karlan BY. Ovarian cancer. Nat Rev Dis Primers 2016;2:16061.
16. Markman M, Federico M, Liu P, Hannigan E, Alberts D. Significance of early changes in the serum CA‑125 antigen level on overall survival in advanced ovarian cancer. Gynecol Oncol 2006;103:195-8.
17. Fung MKL, Cheung HW, Wong HL, Yuen HF, Ling MT, Chan KW, et al. MAD2 expression and its significance in mitotic checkpoint control in testicular germ cell tumour. Biochim Biophys Acta 2007;1773:821-32.
18. Wang X, Jin DY, Ng RW, Feng H, Wong YC, Cheung AL, et al. Significance of MAD2 expression to mitotic checkpoint control in ovarian cancer cells. Cancer Res 2002;62:1662-8.
19. Prencipe M, Fitzpatrick R, Gorman S, Tosetto M, Klinger R, Furlong F, et al. Cellular senescence induced by aberrant MAD2 levels impacts on paclitaxel responsiveness in vitro. Br J Cancer 2009;101:1900.
20. Sudo T, Nitta M, Saya H, Ueno NT. Dependence of paclitaxel sensitivity on a functional spindle assembly checkpoint. Cancer Res 2004;64:2502-8.
21. Gascoigne KE, Taylor SS. Cancer cells display profound intra-and interline variation following prolonged exposure to anti‑mitotic drugs. Cancer Cell 2008;14:111-22.
22. Furlong F, Fitzpatrick P, O’Toole S, Phelan S, McGrogan B, Maguire A, et al. Low MAD2 expression levels associate with reduced progression-free survival in patients with high-grade serous epithelial ovarian cancer. J Pathol 2012;226:746-55.
23. Zannini L, Delia D, Buscemi G. CHK2 kinase in the DNA damage response and beyond. J Mol Cell Biol 2014;6:442-57.
24. Alkema N, Tomar T, van der Zee AG, Everts M, Meersma GJ, Hollema H, et al. Checkpoint kinase 2 (Chk2) supports sensitivity to platinum-based treatment in high grade serous ovarian cancer. Gynecol Oncol 2014;133:591-8.
25. Liefers-Visser J, Meijering R, Meyers A, van der Zee A, de Jong S. IGF system targeted therapy: Therapeutic opportunities for ovarian cancer. Cancer Treat Rev 2017;60:90-9.
26. Deo A, Chaudhury S, Kannan S, Rekhi B, Maheshwari A, Gupta S, et al. IGF1R predicts better survival in high-grade serous epithelial...
ovarian cancer patients and correlates with hCtr1 levels. Biomark Med 2019;13:511-21.

27. Smith WL. Prostanoid biosynthesis and mechanisms of action. Am J Physiol Renal Physiol 1992;263:F181-91.

28. Alves MR, Do Amaral NS, Marchi FA, Silva Fil, Da Costa AA, Carvalho KC. Prostaglandin D2 expression is prognostic in high-grade serous ovarian cancer. Oncol Rep 2019;41:2254-64.

29. Scully J, van Zyl B, Gulliver D, Otton G, Jaaback K, Lombard J, et al. Nucleotide excision repair protein ERCC1 and tumour-infiltrating lymphocytes are potential biomarkers of neoadjuvant platinum resistance in high grade serous ovarian cancer. Gynecol Oncol 2018;151:306-10.

30. Cancer Genome Atlas Research Network. Integrated genomic analyses of ovarian carcinoma. Nature 2011;474:609-15.

31. Brown CW, Brodsky AS, Freiman RN. Notch3 overexpression promotes anoikis resistance in epithelial ovarian cancer via upregulation of COL4A2. Mol Cancer Res 2015;13:78-85.

32. Jung JG, Shih IM, Park JT, Gerry E, Ayhan A, et al. Ovarian cancer chemoresistance relies on the stem cell reprogramming factor PBX1. Cancer Res 2016;76:6351‑61.

33. Jung SG, Kwon YD, Song JA, Back MJ, Lee SY, Lee C, et al. Prognostic significance of Notch 3 gene expression in ovarian serous carcinoma. Cancer Sci 2010;101:1977‑83.

34. Rahman MT, Nakayama K, Rahman M, Katagiri H, Katagiri A, Ishibashi T, et al. Notch3 overexpression as potential therapeutic target in advanced stage chemoresistant ovarian cancer. Am J Clin Pathol 2012;138:535-44.

35. Rekbi B, Deodhar KK, Menon S, Maheshwari A, Bajpai J, Ghosh J, et al. Napsin A and WT 1 are useful immunohistochemical markers for differentiating clear cell carcinoma ovary from high-grade serous carcinoma. APMIS 2018;126:45‑55.

36. Filmus J, Selleck SB. Glypicans: Proteoglycans with a surprise. J Clin Invest 2001;108:497‑501.

37. Grisaru S, Cano‑Gauci D, Tee J, Filmus J, Rosenblum ND. Glypican‑3 modulates BMP- and FGF-mediated effects during renal branching morphogenesis. Dev Biol 2001;231:31‑46.

38. De Cat B, Muyldermans SY, Coomans C, Degeest G, Vanderschueren B, Creemers J, et al. Processing by proprotein convertases is required for glypican-3 modulation of cell survival, Wnt signaling, and gastrulation movements. J Cell Biol 2003;163:625‑35.

39. Pellegri M, Pilia G, Pantano S, Lucchini F, Uda M, Fumi M, Cao A, et al. Gpc3 expression correlates with the phenotype of the Simpson-Golabi-Behmel syndrome. Dev Dyn 1998;213:431‑9.

40. Maeda D, Ota S, Takazawa Y, Aburatani H, Nakagawa S, Yano T, et al. Glypican-3 expression in clear cell adenocarcinoma of the ovary. Mod Pathol 2009;22:824‑32.

41. Vassalli G. Aldehyde dehydrogenases: Not just markers, but functional regulators of stem cells. Stem Cells Int 2019;2019:3904645.

42. Kuroda T, Hirohashi Y, Torigoe T, Yasuda K, Takahashi A, Asanuma H, et al. ALDH1-high ovarian cancer stem-like cells can be isolated from serous and clear cell adenocarcinoma cells, and ALDH1 high expression is associated with poor prognosis. PLoS One 2013;8:e65158.

43. Zanatta A, Rocha AM, Carvalho FM, Pereira RM, Taylor HS, Motta EL, et al. The role of the Hoxa10/HOXA10 gene in the etiology of endometriosis and its related infertility: A review. J Assist Reprod Genet 2010;27:701‑10.

44. Li B, Jin H, Yu Y, Gu C, Zhou X, Zhao N, et al. HOXA10 is overexpressed in human ovarian clear cell adenocarcinoma and correlates with poor survival. Int J Gynecol Cancer 2009;19:1347‑52.

45. Wang W, Xue Y, Zhou S, Kuo A, Cairns BR, Crabtree GR. Diversity and specialization of mammalian SWI/SNF complexes. Genes Dev 1996;10:2117‑30.

46. Katagiri A, Nakayama K, Rahman MT, Rahman M, Katagiri H, Nakayama N, et al. Loss of ARID1A expression is related to shorter progression‑free survival and chemoresistance in ovarian clear cell carcinoma. Mod Pathol 2012;25:282‑8.

47. Sato E, Nakayama K, Razia S, Nakamura K, Ishikawa M, Minamoto T, et al. ARID1B as a Potential Therapeutic Target for ARID1A‑Mutant Ovarian Clear Cell Carcinoma. International journal of molecular sciences 2018;6:1710‑30.

48. Kato N, Toukairin M, Asanuma I, Motoyama, T. Immunocytochemistry for hepatocyte nuclear factor-1beta (HNF-1beta): A marker for ovarian clear cell carcinoma. Diagn Cytopathol 2007; 35:193‑7.