Nuclear Localization of SMAD3 as an Independent Predictor of Recurrence in Ovarian Adult Granulosa Cell Tumor

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ABSTRACT

Background & Objective: Adult granulosa cell tumors (AGCTs) are potentially malignant ovarian neoplasms with a well-known tendency for local spread and recurrence, years after prolonged follow-up. This study investigated the immunohistochemical (IHC) expression of SMAD3 (mothers against decapentaplegic homolog 3) in AGCTs to evaluate its association with a number of confirmed AGCT prognostic variables.

Materials & Methods: Upon database search, the clinicopathological data, slides, and paraffin blocks of 35 AGCTs were retrospectively retrieved from archives, then examined histopathologically, staged, and stained immunohistochemically using anti-SMAD3. After H scoring of "SMAD3", the clinicopathological associations were investigated in positive- and negative-SMAD3 expression groups using appropriate statistical methods. Regression analysis was performed to define independent predictors of recurrence in AGCT.

Results: SMAD3 was actively expressed in the nuclei of 51.4% of AGCTs. It was significantly associated with tumor recurrence, capsular rupture, and size (P=0.011, 0.018, and 0.028, respectively), but not with age, presentation, laterality, stage, tumor morphological pattern, or mitotic index. Capsular rupture and tumor size were defined as highly significant ($P \le 0.001$), as well as SMAD3+ve expression and FIGO stage as significant independent predictors of recurrence (P=0.05 and 0.049, respectively) in AGCT.

Conclusion: SMAD3 is actively expressed in the tumor cell nuclei of around one half of AGCTs and this expression associates with high propensity for tumor recurrence, capsular rupture, and increasing tumor size. Along with the other observed independent predictors of recurrence, SMAD3 may provide an outline to direct discovery of new risk-stratification criteria as well as therapeutic targets for AGCTs.

Keywords: AGCT, Immunohistochemistry, Independent predictors, Recurrence, SMAD3

Introduction

Adult granulosa cell tumor (AGCT) is a clinically and molecularly distinct subtype of ovarian neoplasm that originates from the ovarian sex-cord cells and constitutes around 3-5% of all ovarian malignant neoplasms. These tumors usually arise in peri-menopausal or post-menopausal females, and peak at the age of 50-55 years **(1-3)**.

In spite of their indolent growth and the generally favorable prognosis, local spread and recurrence can affect 10-30% of AGCT patients, especially after extended latency periods, and these factors are notably associated with poor survival rates **(4)**. In addition to the International Federation of Gynecology and Obstetrics (FIGO) staging system, numerous studies have tried to outline the prognostic predictors in AGCT; however, their role has not been obviously demarcated ow-

ing to the infrequency of the AGCT and the necessity to follow up the patients for many years. Thus, the discovery of consistent biological markers in AGCTs is required to facilitate stratifying AGCT patients into different risk groups and hence, forecast which patient may have a higher recurrence risk. This may allow further fine-tuning of the adjuvant therapy **(3)**.

Although 95-97% of AGCTs harbor recurrent forkhead box (FOX) L2 c.C402G/p.C134W hotspot mutations that were confirmed as key factors in the pathogenesis of AGCTs **(5)**, the molecular mechanism by which FOXL2 (C134W) contributes to tumorigenesis is not well-known **(6,7)**. Noteworthy, granulosa cell proliferation seems to be dependent on different signaling pathways including the adenyl cyclase-/cAMP/protein kinase A (PKA) pathway, mitogen

activated protein kinase (MAPK) and phosphatidyl inositol 3-kinase- PI3K/AKT pathway, and the transforming growth factor beta (TGF-β) signaling pathway. Any alteration in these pathways can lead to the unrestrained granulosa cell proliferation and the subsequent development of AGCT. Thus, studying these pathways may help developing new therapeutic agents for AGCT particularly in the setting of recurrence (1,3,8,9).

The "mothers against decapentaplegic homolog 3" (SMAD3) is a 48,080 Dalton protein encoded by a gene located on chromosome 15q22.33. It belongs to a family of proteins referred to as SMADs. These proteins mediate the signals sponsored by the TGF-β superfamily of cytokines to control cell differentiation, division, and apoptosis. Founded on its vital contribution to TGF-β signaling pathway, SMAD3 was connected to the development and progression of many malignant processes. Furthermore, SMAD3 was linked to the MAPK/ERK pathway, principally to the activation of mitogen-activated protein kinase-kinase-1 (MEK1) (9-11). More significantly, a novel evidence has been designated to molecular and functional interplays between FOXL2 and SMAD3, proposing that SMAD3 stimulation might function as an important convergence point that dysregulates TGF-β superfamily signaling and elicits genetic deviations in human GCT (6,7,10). Thus, detection of SMAD3 in AGCT tissues may provide novel prognostic and therapeutic insights to ACGT. Considering these, this work was intended to explore the immunohistochemical (IHC) expression of SMAD3 in AGCTs and to discover if there is any association between its expression and a number of the confirmed AGCT prognostic variables. Moreover, the prognostic predictors of recurrence in AGCT were further defined.

Materials and Methods

Patient Selection and Data Collection

This retrospective study included 35 female patients diagnosed with AGCT during the period from January 2016 to December 2020. The cases were retrieved from the Pathology Department archives based on an electronic database search for the diagnosis of AGCT. Following approval by the Institutional Research Board (IRB) of the author's institution and obtaining consents according to the rules validated by our institutional IRB, the hematoxylin-and-eosin (H&E) slides, the IHC-stained slides for sex-cord markers: inhibin-alpha and calretinin (routinely conducted stains to confirm diagnosis according to our laboratory protocols) and the formalin-fixed, paraffin embedded (FFPE) tissue blocks were extracted from our department archives. Data including age at the surgery time, presentation, tumor laterality, tumor size (the largest dimension in cm), capsular rupture, nodal and distant metastasis, peritoneal involvement, positivity of peritoneal/pelvic fluid samples (ascites or peritoneal washi-

ngs), and history of recurrence were retrieved from the surgical and gross pathology reports. None of the patients had a history of pre-operative chemo-radiotherapy. A tumor was defined as primary if the patient was first presented with no previous history of adnexal masses. For any case with recurrence, the recurrent tumor was matched with the primary tumor and both were considered as a single case (4).

Histopathologic evaluation and staging

To confirm diagnosis of AGCT, the H&E slides and the inhibin-alpha and calretinin-stained slides were reviewed for all selected cases and re-evaluated in accordance to the World Health Organization diagnostic criteria (12). The main histopathologic pattern of each tumor was detected and the mitotic count was evaluated by counting the number of unequivocal mitotic figures per 10 high-power fields (HPFs) in the tumor areas that harbor the maximum density of mitoses screened at low magnification. A cutoff at 4 mitoses/10 HPF was adopted to divide tumors into low- and high-mitotic indices categories (3). Staging was accomplished according to the FIGO system (2014) (13).

Immunohistochemistry

Immunohistochemistry (IHC) was performed with anti-human SMAD3 monoclonal antibody (Elabscience, mouse, IgG, Cat.AB-22176, dilution 1:150; incubated at 20-37°C for 1-2 h), using the standard horseradish peroxidase (HRP) technique on a 3-4 micrometer-cut, AGCT paraffin sections on coated slides. Diaminobenzidine was applied as a chromogen and hematoxylin for counterstaining. H scoring of SMAD3 expression was done semi-quantitively using x20 objective of light microscope (Leica DM500) and combining both the intensity of staining and the percentage of stained tumor cells to the total number of tumor cells. The cases were considered negative for 0% staining and positive for any nuclear staining (as per data sheet recommendation). Positive cases were divided as follows: score+1 (weak staining of any percentage or focal moderate or strong staining in 1-20% of the tumor cells), score+2 (moderate or strong staining in >20-70% of the tumor cells), and score+3 (moderate or strong staining in >70% of the tumor cells) (14).

Statistical analysis

For the statistical analysis, SPSS software version 23 (IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.) was applied. The Kolmogorov-Smirnov test was run to evaluate the normality of data. The quantitative data of normal distribution were designated as means ±standard deviation, whilst the qualitative data were defined as frequencies and percentages. The independent-samples t-test and Mann-Whitney U test were applied for comparing continuous variables between the groups, and the Chi-square test and the Fisher's exact test (in case of anticipated count less than 5) were conducted for the categorical variables. To discern the independent predictors of tumor recurrence, regression analysis was done. A P-

value less than or equal to 0.05 was established as the level of significance in all tests and a P-value below 0.001 was considered as highly significant.

The clinicopathological criteria of the 35 AGCTs and the comparison of SMAD3-positive and -negative expression groups with the studied variables are emphasized in Table 1.

Results

Table 1. The clinicopathological criteria of the 35 adult granulosa cell tumors and the comparison of SMAD-3-positive and -negative expression-groups with the studied variables

Variables	All AGCTs (35, 100%)	SMAD-3-positive (18, 51.4%)	SMAD-3-negative (17, 48.6%)	P-value
Age at surgery/year				
Range	29-73	32-73	29-63	0.969
Mean±SD	44.3±11.8	44.3±13.2	44.2±10.3	
Presenting symptoms/signs (no, %)				
Pelvi-abdominal mass	22(62.9)	12 (66.7)	10 (58.8)	
Vaginal bleeding	8 (22.9)	4 (22.2)	4 (23.5)	0.838
Other	5 (14.3)	2 (11.1)	3 (17.6)	
Laterality (no, %)				
Unilateral	33 (5.7)	16 (88.9)	17 (100)	0.257
Bilateral	2 (94.3)	2 (11.1)	0 (0)	
Size (largest dimension)/ cm.				
Range	5.5-15	6.5-14	6-15	0.028*
Mean±SD	9.5±2.7	10.4±2.7	8.5±2.3	
Capsular rupture (no, %)				
No	24 (68.6)	9 (50)	15 (88.2)	0.018*
Yes	11 (31.4)	9 (50)	2 (11.8)	
Recurrence (no, %)				
No	26 (74.3)	10 (55.6)	16 (94.1)	0.011*
Yes	9 (25.7)	8 (44.4)	1 (5.9)	
Stage (no, %)				
I and II	23 (65.7)	11 (61.1)	12 (70.6)	
III and IV	8 (22.9)	5 (27.8)	3 (17.6)	0.773
Not assessed	4 (11.4)	2 (11.1)	2 (11.8)	
Main histopathologic pattern (no, %)				
Microfollicular	5 (14.3)	3 (16.7)	2 (11.8)	
Diffuse	8 (22.9)	5(27.8)	3 (17.6)	0.652
Mixed	22 (62.9)	10 (55.6)	12 (70.6)	
Mitosis/10 HPFs (no, %)				
<4	30 (85.7)	16(88.9)	14(82.4)	0.472
≥4	5 (14.3)	2(11.1)	3(17.6)	

AGCT; adult granulosa cell tumor, no; number, %; percentage, HPFs; high-power fields, *P-value is significant if ≤0.05.

Clinicopathological criteria

The study included 35 female patients diagnosed with AGCTs. The mean patients' age was 44.3 years, most of whom were presented with a pelvi-abdominal mass, followed by vaginal bleeding, while a small percentage (14.3%) was presented with other symptoms including: infertility (2 cases), virilization, hirsutism, and acute abdominal pain (one case each). Most of the ovarian masses were unilateral (94.3%), with a mean size of 9.5 cm, and 31.4% of tumors revealed evidence of capsular rupture. About 25.7% of patients had recurrence in a range from 6 months to 5 years following the primary surgery. Most cases (65.7%) were presented in early stages (I and II), and less likely in a late stage (22.9%; III and IV), while in the remainder of cases, the stage was not assessed. On microscopic examination, most of the tumors (62.9%) revealed a mixed growth pattern, followed by the diffuse, then the microfollicular patterns. About 14.3%

of cases showed more than 4 mitotic figures per 10 examined HPFs.

SMAD3 expression, localization, and comparison with prognostic variables

Using the abovementioned H score, nuclear SMAD3 expression was observed in 18/35 (51.4%) of AGCTs, classified as: 22.9% of score+3 (8 cases), 14.3% of score+2 (5 cases), and 14.3% of score+1 (5 cases) (Figure 1).
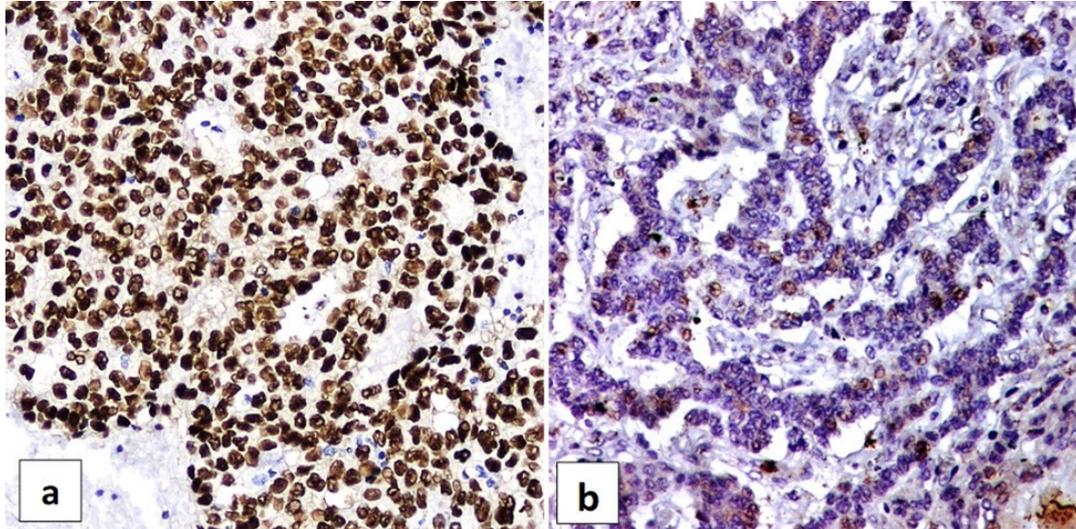
Figure 1. Nuclear SMAD-3 expression in adult granulosa cell tumor (AGCT). A case of AGCT with dominant microfollicular pattern showing diffuse nuclear expression of SMAD-3, H score+3 (a), and another case with mixed patten showing focal SMAD-3 expression within the trabecular foci, H score+1 (b); (Diaminobenzidine, x250)

The statistical analysis revealed significant associations between SMD3-positive expression and the tumor recurrence, capsular rupture, and tumor size (*P*=0.011, 0.018, and 0.028, respectively), as SMD3-+ve tumors showed a recurrence rate of 44.4% compared to a recurrence rate of 5.9% in SMD3-ve tumors; in other words, 8/9 (88.9%) of recurrent tumors were SMAD3+ve compared to 10/26 (38.5%) of the non-recurrent tumors. Half of SMD3+ve tumors showed capsular rupture compared to 11.8% of SMD3-ve tumors (i.e., 9/11; 81.8% of ruptured tumors were SMAD3+ve compared to 9/24; 37.5% of the non-ruptured tumors) and the mean largest dimension of the former group was larger than the later (10.4 vs. 8.5 cm).

In contrast, there were no statistical associations between SMAD3 expression and the other prognostic variables including the age, presentation, laterality, and FIGO stage, in addition to the histopathologic criteria including the main morphologic pattern of the tumor and the mitotic index.

Independent predictors of tumor recurrence

Regression analysis (Table 2) revealed that capsular rupture and tumor size were highly significant independent predictors of recurrence (*P*≤0.001), whilst SMAD3+ve expression and FIGO stage were significant predictors of recurrence (*P*=0.05 and 0.049, respectively) in AGCT. In this analysis, the observed cumulative probability of recurrence was found to increase with SMD3+ve expression, late FIGO stages, presence of capsular rupture, and a tumor size larger than 9.5 cm (reference groups).

Table 2. Regression analysis for independent predictors of recurrence in adult granulosa cell tumor.

Independent predictors		Beta	P-value	95%CI
SMD3 expression	Positive (r), Negative	0.358	0.05*	-.008- 0.557
FIGO stage	I and II, III and IV (r)	0.273	0.049*	-0.043- 0.389
Capsular rupture	No, Yes (r)	0.728	≤0.001**	0.457- 0.914
Size (largest dimension)/cm.	<9.5, ≥9.5 (r)	0.736	≤0.001**	0.083-0 .163

(r); reference group, CI; confidence interval, *P-value is significant if ≤0.05 and is **highly significant if ≤0.001.

Discussion

AGCTs are known to be potentially malignant tumors that harbor challenging intra-operative and post-operative treatment decisions especially in the spotlight of the high recurrence rates that may be detectable after lengthy periods of follow-up. The gold standard for the management of either a primary or a relapsing AGCT is surgery, meanwhile the chemo- and radiotherapy are used only to manage patients with non-resectable tumors or patients with clinically advanced neoplasms. Although tumor stage is the most important determinant for prognosis, about 33% of patients diagnosed with AGCT suffer relapses, usually as disseminated peritoneal metastasis that usually occurs within 4 to 7 years after being diagnosed, thereby causing mortality in 50% of relapsed patients (2). The treatment options for relapse including systemic chemotherapy, secondary cytoreductive surgery or palliative localized radiation therapy, and hyperthermic intraperitoneal chemotherapy have not yet been standardized due to the rarity of this disease (15). Therefore, novel molecular biomarkers should be elaborated to define patients with a high-risk for relapse or recurrence.

A recent study on AGCTs showed that when FOXL2C134W and SMAD3 become overexpressed, they affect the expression of about 717 genes. Such genes comprise many FOXL2 target genes for example SMARCA4, TGFB2, HSPG2, NFKBIA, and MKI67. These effects augment numerous neoplastic processes including the remodeling of chromatin, the apoptotic pathways, the morphogenesis of tissues, and the tyrosine-kinase receptor pathway (16) that control epithelial-to-mesenchymal transition, stemness, and oncogenesis in AGCT (7). As a developing molecular biomarker, the IHC-expression of SMAD3 in AGCTs was addressed in a few reports, and the high expression of SMAD3 independently predicted an increased recurrence probability and a shorter disease-free survival, notably in early stage AGCT (14,17).

In the current study, SMAD3 was expressed in 51.4% of AGCTs, and its expression was significantly associated with high rates of tumor recurrence. Most of the recurrent tumors (88.9% vs. 38.5%) and most of the tumors with capsular rupture (81.8% vs. 37.5%) expressed SMAD3. Moreover, these positive tumors had a larger mean tumor size compared to the SMAD-negative tumors, indicating the participation of SMAD3 in stimulating AGCT growth. These data lend support to the data provided by Sakr et al. (17), who reported SMAD3 expression in all recurrent AGCTs compared to 27% of the non-recurrent tumors. Thus, the IHC assessment of SMAD3 may be a valuable parameter to counsel patients after surgery regarding the possibility of recurrence, and the necessity for closer surveillance or chemo- or radiotherapy. These data also might validate SMAD3 to be a forthcoming target for therapy (17). In this regard, SMAD3 may be additionally included in the predictive model for recurrence proposed by Nosov et al. (18) which included patients aging below 43.6 years whose tumors had a high inhibin-alpha expression, a high Ki-67 proliferation index, and who may benefit from prolonged surveillance and adjuvant chemotherapy. In this work, regression analysis disclosed that capsular rupture and tumor size were highly significant independent predictors of recurrence in AGCT, whilst SMAD3+ve expression and FIGO stage were significant predictors of recurrence, thereby adding more predictive factors for AGCT recurrence.

Meanwhile, we were not able to find any association between SMAD3 expression and patient's age or presenting symptoms, tumor laterality and stage, or the histopathologic pattern and mitotic index among the study cohort. In the same vein, Anttonen et al. (14) did not find any association between SMAD3 protein expression and several prognostic factors including the patient's age, if the patient is pre-or post-menopausal at diagnosis, the tumor subtype, the clinical stage, the degree of nuclear atypia, and the mitotic index.

On molecular basis, SMADs are known to be nucleocytoplasmic shuttling proteins and the nuclear existence of SMAD3 is firmly linked to its tumor-promoting activities. In fact, SMAD2 and 3 are crucial signal transducers that function in TGF-β signaling, and their transcriptional activities are mediated by two processes: reversible phosphorylation, and nucleocytoplasmic shuttling. Therefore, the Ran-Binding Protein 3 (RanBP3)-mediated selective nuclear export of SMAD2/3 suppresses the TGF-β signaling pathway; on the contrary, the inhibition of RanBP3 enhances the TGF-β-induced transcriptional responses via maintaining the nuclear localization of SMAD2/3 (19,20). In the current study, SMAD3 exhibited mainly a nuclear localization in AGCT cells, indicating that it is in its active state. Likewise, it has been documented that growing AGCT cells in mouse models express nuclear SMAD3 in conjunction with activin and inhibin (8). Similarly, the nuclei of the primordial granulosa cells express SMAD3 together with the cell cycle regulating proteins viz cyclin D2 (CCND2) and P27, where SMAD3 acts as a transcription factor (11). In some other studies, SMAD3 was detected mainly in the cytoplasm (17) or in the nucleus of both normal ovarian follicles and AGCTs with only low levels in the cytoplasm (14). However, the cellular localization of SMAD3 in these studies may be dependent on the type of the anti-SMAD3 antibody used and the nature of neoplastic tissue tested as well.

Conclusion

This study verifies that SMAD3 is actively expressed in the tumor cell nuclei of around half of the AGCTs and this expression associates with high propensity for tumor recurrence, capsular rupture, and increasing

tumor size, regardless of the patient's age, symptoms, FIGO stage, or the histologic criteria of the tumor. Along with the other observed independent predictors of recurrence, SMAD3 may provide an outline to direct discovery of new risk-stratification criteria as well as therapeutic targets for AGCTs.

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Conflict of Interest

The author declares that no relevant financial affiliations or conflicts of interest to disclos.

Ethics Approval

The study was conducted upon obtaining ethical approval from the Institutional Research Board (IRB) at Faculty of Medicine, Mansoura University (Code: R.21.04.1299.R1). Informed consents were obtained from patient according to the protocols approved by the local IRB. All procedures followed the current revision of Helsinki Declaration of medical research involving human subjects.

References

1. Kottarathil VD, Antony MA, Nair IR, Pavithran K. Recent advances in granulosa cell tumor ovary: a review. Indian J Surg Oncol. 2013;4(1):37-47. [DOI:10.1007/s13193-012-0201-z]

2. Färkkilä A, Haltia UM, Tapper J, McConechy MK, Huntsman DG, Heikinheimo M. Pathogenesis and treatment of adult-type granulosa cell tumor of the ovary. Ann Med. 2017;49(5):435-47. [DOI:10.1080/07853890.2017.1294760]

3. Babarović E, Franin I, Klarić M, Ferrari AM, Karnjuš-Begonja R, Eminović S, Ostojić DV, Vrdoljak-Mozetič D. Adult granulosa cell tumors of the ovary: A Retrospective study of 36 FIGO stage I cases with emphasis on prognostic pathohistological features. Anal Cell Pathol (Amst). 2018; 2018:9148124. [DOI:10.1155/2018/9148124]

4. da Cruz Paula A, da Silva EM, Segura SE, Pareja F, Bi R, Selenica P, Kim SH, Ferrando L, Vahdatinia M, Soslow RA, Vidal A, Gatius S, Przybycin CG, Abu-Rustum NR, Matias-Guiu X, Rubin BP, Reis-Filho JS, DeLair DF, Weigelt B. Genomic profiling of primary and recurrent adult granulosa cell tumors of the ovary. Mod Pathol. 2020;33(8):1606-17. [DOI:10.1038/s41379-020-0514-3]

5. Jamieson S, Butzow R, Andersson N, Alexiadis M, Unkila-Kallio L, Heikinheimo M, Fuller PJ, Anttonen M. The FOXL2 C134W mutation is characteristic of adult granulosa cell tumors of the ovary. Mod Pathol. 2010;23(11):1477-85. [DOI:10.1038/modpathol.2010.145]

6. Belli M, Secchi C, Stupack D, Shimasaki S. FOXO1 Negates the cooperative action of FOXL2C134W and SMAD-3 in CYP19 Expression in HGrC1 cells by sequestering SMAD-3. J Endocr Soc. 2019;3(11):2064-81. [DOI:10.1210/js.2019-00279]

7. Weis-Banke SE, Lerdrup M, Kleine-Kohlbrecher D, Mohammad F, Sidoli S, Jensen ON, Yanase T, Nakamura T, Iwase A, Stylianou A, Abu-Rustum NR, Aghajanian C, Soslow R, Da Cruz Paula A, Koche RP, Weigelt B, Christensen J, Helin K, Cloos PAC. Mutant FOXL2C134W hijacks SMAD4 and SMAD2/3 to drive adult granulosa cell tumors. Cancer Res. 2020;80(17):3466-79. [DOI:10.1158/0008-5472.CAN-20-0259]

8. Kim SY, Ebbert K, Cordeiro MH, Romero MM, Whelan KA, Suarez AA, Woodruff TK, Kurita T. Constitutive activation of PI3K in oocyte induces ovarian granulosa cell tumors. Cancer Res. 2016;76(13):3851-61. [DOI:10.1158/0008-5472.CAN-15-3358]

9. Ding Q, Jin M, Wang Y, Liu J, Kalds P, Wang Y, Yang Y, Wang X, Chen Y. Transactivation of miR-202-5p by steroidogenic Factor 1 (SF1) induces apoptosis in goat granulosa cells by targeting TGFβR2. cells. 2020;9(2):445. [DOI:10.3390/cells9020445]

10. Fang X, Gao Y, Li Q. SMAD-3 Activation: A converging point of dysregulated TGF-Beta superfamily signaling and genetic aberrations in granulosa cell tumor development? Biol Reprod. 2016;95(5):105. [DOI:10.1095/biolreprod.116.143412]

11. Granados-Aparici S, Hardy K, Franks S, Sharum IB, Waite SL, Fenwick MA. SMAD-3 directly regulates cell cycle genes to maintain arrest in granulosa cells of mouse primordial follicles. Sci Rep. 2019; 9(1):6513. [DOI:10.1038/s41598-019-42878-4]

12. Zaloudek CJ, Mooney EE, Staats PN, Young RH. Sex cord-stromal tumors - pure sex cord tumors, In: Kurman RJ, Carcangiu ML, Herrington CS, Young RH, (eds). WHO Classification of Tumors of Female Reproductive Organs. 4th edition. Vol. 6 IARC: Lyon, France; 2014 pp 50-3

13. Prat J, FIGO Committee on Gynecologic Oncology. FIGO's staging classification for cancer of the ovary, fallopian tube, and peritoneum: abridged republication. J Gynecol Oncol. 2015;26(2):87-9. [DOI:10.3802/jgo.2015.26.2.87]

14. Anttonen M, Pihlajoki M, Andersson N, Georges A, L'hôte D, Vattulainen S, Färkkilä A, Unkila-Kallio L, Veitia RA, Heikinheimo M. FOXL2, GATA4, and SMAD-3 co-operatively modulate gene expression, cell viability and apoptosis in ovarian granulosa cell tumor cells. PLoS One. 2014;9(1):e85545. [DOI:10.1371/journal.pone.0085545]

15. Yasukawa M, Matsuo K, Matsuzaki S, Dainty LA, Sugarbaker PH. Management of recurrent granulosa cell tumor of the ovary: Contemporary literature review and a proposal of hyperthermic intraperitoneal chemotherapy as novel therapeutic option. J Obstet Gynaecol Res. 2021;47(1):44-51. [DOI:10.1111/jog.14494]

16. Secchi C, Benaglio P, Mulas F, Belli M, Stupack D, Shimasaki S. FOXO1 mitigates the SMAD-3/FOXL2C134W transcriptomic effect in a model of human adult granulosa cell tumor. J Transl Med. 2021;19(1):90. [DOI:10.1186/s12967-021-02754-0]

17. Sakr S, Abdulfatah E, Thomas S, Al-Wahab Z, Beydoun R, Morris R, Ali-Fehmi R, Bandyopadhyay S. Granulosa cell tumors: Novel predictors of recurrence in early-stage patients. Int J Gynecol Pathol. 2017;36(3):240-52. [DOI:10.1097/PGP.0000000000000325]

18. Nosov V, Silva I, Tavassoli F, Adamyan L, Farias-Eisner R, Schwartz PE. Predictors of recurrence of ovarian granulosa cell tumors. Int J Gynecol Cancer. 2009;19(4):628-33. [DOI:10.1111/IGC.0b013e3181a48a6f]

19. Dai F, Lin X, Chang C, Feng XH. Nuclear export of Smad2 and SMAD-3 by RanBP3 facilitates termination of TGF-beta signaling. Dev Cell. 2009;16(3):345-57. [DOI:10.1016/j.devcel.2009.01.022]

20. Amarnath S, Agarwala S. Cell-cycle-dependent TGFβ-BMP antagonism regulates neural tube closure by modulating tight junctions. J Cell Sci. 2017;130(1):119-31. [DOI:10.1242/jcs.179192].

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