Peroxisome proliferator-activated receptor-α expression is associated with histological type in human gastric carcinoma

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Abstract. Gastric carcinoma is one of the most common types of cancer worldwide and a leading cause of cancer-related mortality. Gastric carcinoma is histologically subdivided into differentiated and undifferentiated carcinoma, with the latter including poorly differentiated carcinoma and signet ring cell carcinoma (SRCC). Poorly differentiated carcinoma and SRCC have a worse prognosis compared with differentiated carcinoma. Peroxisome proliferator-activated receptors (PPARs) are nuclear hormone receptors and the PPAR-α subtype regulates important cellular functions, including cell proliferation, energy metabolism, oxidative stress, immune responses and cell differentiation. The aim of the present study was to elucidate the associations between clinicopathological factors and PPAR-α expression in patients with gastric carcinoma. The immunohistochemical staining of specimens obtained from 57 patients showed that PPAR-α expression was slightly weaker in undifferentiated carcinoma than in differentiated carcinoma (P<0.01). PPAR-α expression also significantly differed between poorly differentiated carcinoma (both positive and negative: 14/20, 70%) and SRCC (not expressed: 0/7, 0%) (P<0.01). However, PPAR-α expression was not significantly affected by age, lymph node invasion, venous invasion, lymph node metastasis, depth of invasion or stage. Collectively, the present results demonstrated that the downregulated expression of PPAR-α may play a key role in the biological transformation of tumors. Therefore, PPAR-α appears to be an important protein related to histology and may hold promise as a prognostic marker. Further studies with a larger number of subjects are needed to elucidate the relationship between PPAR-α expression and tumor progression and to analyze long-term clinical survival.

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Introduction

Gastric carcinoma is one of the most common types of cancer and the main causes of cancer-related mortality worldwide (1). According to the Japanese Gastric Cancer Classification, gastric adenocarcinoma is histologically subdivided into differentiated and undifferentiated types, and patients with undifferentiated tumors generally have a poorer prognosis (2-4). Diffuse types of gastric carcinoma, consisting of infiltration by single cells or small groups of tumor cells, correspond to poorly differentiated gastric carcinoma in the World Health Organization classification and include heterogeneous subtypes, such as signet ring cell carcinoma (SRCC) and non-SRCC (NSRCC) (5). The prevalence of poorly differentiated gastric carcinoma is higher compared with that of well-differentiated gastric carcinoma (6). Furthermore, poorly differentiated carcinoma and SRCC have a worse prognosis than differentiated carcinoma (7,8).

Peroxisome proliferator-activated receptors (PPARs) are nuclear hormone receptors that were initially described as molecular targets for compounds that induce peroxisomal proliferation (9). PPARs regulate the transcription of several genes involved in lipid metabolism, energy utilization and storage (10), and consist of three subtypes (PPAR-α, PPAR-β/δ and PPAR-γ) (11,12). These subtypes may be partially distinguished by their tissue distribution, ligands and target specificities (13-16). PPAR-α is predominantly expressed in tissues that catabolize large amounts of fatty acids, such as the liver, kidneys, and heart (17). Additionally, PPAR-α regulates important cellular functions, including cell proliferation, differentiation, energy metabolism, oxidative stress, inflammation, circadian rhythm, immune responses and cell

differentiation. However, the relationship between the expression of PPAR-α and the histological type of gastric carcinoma currently remains unclear. Furthermore, the biological function of PPAR-α has not yet been elucidated, and the role of PPAR-α expression in gastric carcinoma has not been investigated to date.

Therefore, further studies are needed to clarify these controversial findings and to fully elucidate the function of PPAR-α. The aim of the present study was to examine the associations between PPAR-α expression and clinicopathological factors in gastric carcinoma and assess the usefulness of PPAR-α as a new prognostic marker.

Materials and methods

Clinical samples. A total of 57 patients (42 men and 15 women, with a mean age of 72.1±9.0 years; range, 50-91 years) who were diagnosed with gastric carcinoma at Kagawa University Hospital (Kagawa, Japan) between April 2012 and March 2014 were examined in the present study. Clinicopathological factors were classified according to sex, age, histological type, lymphatic invasion, venous invasion, lymph node metastasis, depth of invasion and stage based on the 15th Edition of Japanese Classification of Gastric Carcinoma (18). Samples obtained from surgical resection for curative treatment included 7 from endoscopic submucosal dissection, 45 from partial gastrectomy and 5 from total gastrectomy. There was one case of distant metastasis. All clinical samples were provided after obtaining written informed consent from the patients. The present study was conducted with the approval of the Institutional Research Ethics Committee of the Kagawa Prefectural University of Health Sciences (Kagawa, Japan; approval no. 215).

Immunohistochemistry. Immunohistochemistry was performed as previously described (19). Briefly, formalin-fixed paraffin-embedded tissues were cut into 4-μm sections. The sections were deparaffined in xylene (Muto Pure Chemicals Co., Ltd.) and rehydrated in ethanol (Muto Pure Chemicals Co., Ltd.). Antigen retrieval was conducted by autoclave heating at 120˚C for 15 min in 0.01 M citrate buffer (pH 6.0) containing 38 mg/dl citric acid monohydrate and 241 mg/dl trisodium citrate dehydrate (Wako Pure Chemical Industries, Ltd.). Endogenous peroxidase activity was blocked using 3% hydrogen peroxide at room temperature for 10 min (Wako Pure Chemical Industries, Ltd.) and non-specific antibody binding using 0.1% skimmed milk at room temperature for 10 min (Wako Pure Chemical Industries, Ltd.). An HRP-labeled monoclonal anti-PPAR-α antibody (cat. no. sc-398394, Santa Cruz Biotechnology, Inc.) was used for the primary antibody reaction. The sections were incubated with primary antibody diluted to 1:200 in PBS at room temperature for 2 h, rinsed three times with PBS and stained with 3,3'-diaminobenzidine tetrahydrochloride substrate (Nichirei Biosciences). The sections were then counterstained with Meyer's hematoxylin, dehydrated, transparentized with xylene, and mounted in malinol. The expression of PPAR-α in cells was examined under a light microscope (BX53; Olympus Corporation) at a magnification of x200. The classification of PPAR-α expression was based on the criteria of Lin *et al* (20). Nuclear PPAR-α expression was assessed using the following scores: Unstained, 0; <25% positive cells, 1+; 25-50% positive cells, 2+; 50-75% positive cells, 3+; and >75% positive cells, 4+. PPAR-α expression levels were measured in the negative (0, 1+ and 2+) and positive (3+ and 4+) groups.

Table I. Clinical characteristics of 57 patients with gastric adenocarcinoma.

Parameters	Patients, n (%)
Sex	
Male	42 (73.7)
Female	15 (26.3)
Age (mean ± standard deviation)	72.1±9.0
Histological type	
Differentiated carcinoma	30 (52.6)
Undifferentiated carcinoma	27 (47.4)
Lymphatic invasion	
Positive	41 (71.9)
Negative	16 (28.1)
Venous invasion	
Positive	36 (63.2)
Negative	21 (36.8)
Lymph node metastasis	
Positive	22 (38.6)
Negative	35 (61.4)
Depth of invasion	
T1a	6 (10.5)
T1b	18 (31.6)
T2	7 (12.3)
T3	14 (24.6)
T4a	11 (19.3)
T4b	1 (1.7)
Stage	
I	26 (45.6)
IIA	5 (8.8)
IIB	9 (15.8)
III	16 (28.1)
IVA	1 (1.7)

Statistical analysis. The associations between immunohistochemical staining and clinicopathological factors were examined using Pearson's χ^2 test or Fisher's exact test. $P<0.05$ was considered to indicate a statistically significant difference. All statistical analyses were performed using SPSS 24.0 software (IBM Corp.).

Results

Clinicopathological characteristics. The characteristics of patients with gastric carcinoma are summarized in Table I. There were 57 patients (42 men and 15 women) with a mean age of 72.1±9.0 years. There were 30 cases of differentiated carcinoma and 27 of undifferentiated carcinoma (20 of poorly

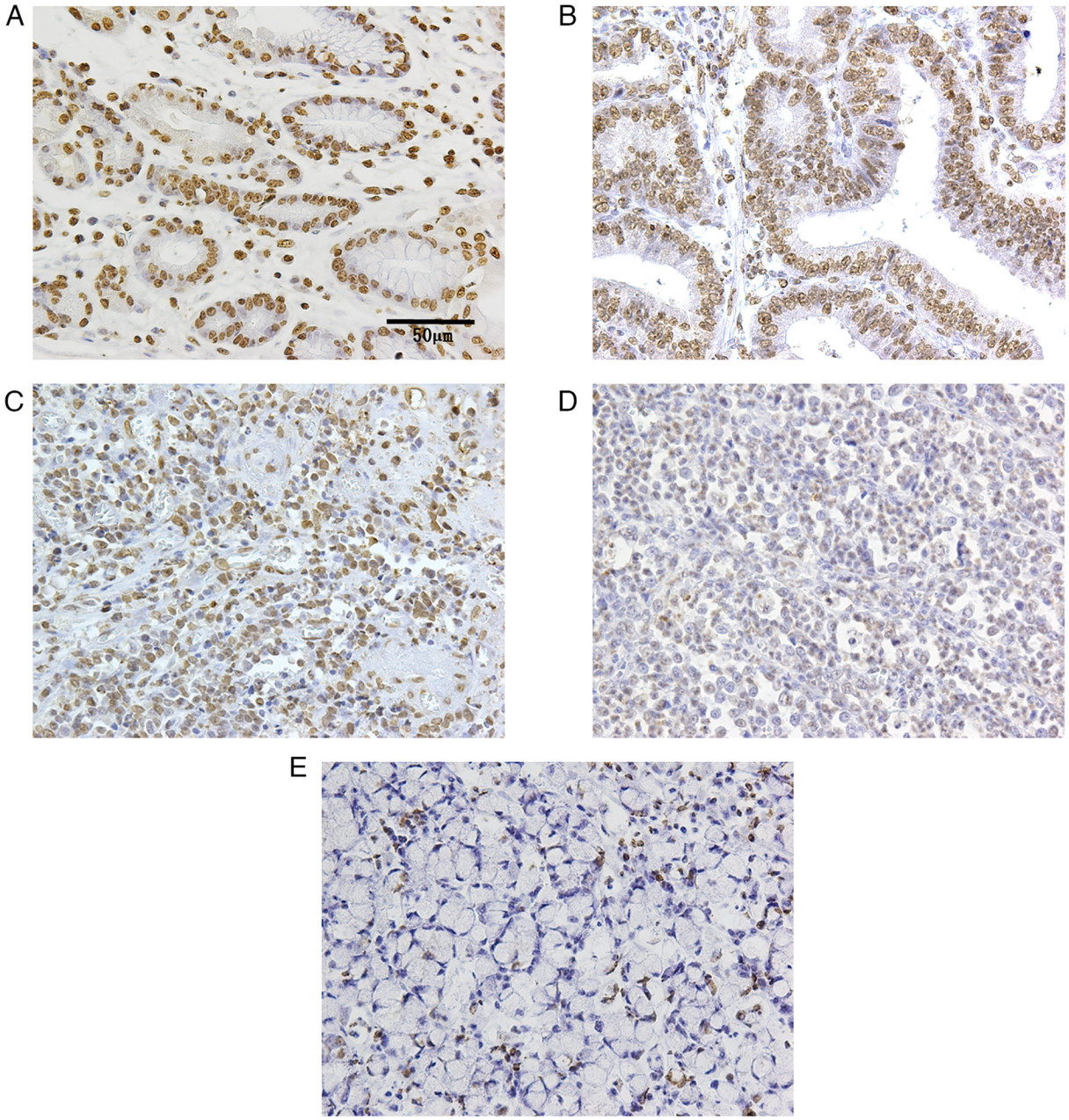

Figure 1. Expression of peroxisome proliferator-activated receptor-α in different histological types of gastric adenocarcinoma. (A) Positive expression in normal epithelial tissue (magnification, x200). (B) Positive expression in differentiated carcinoma (magnification, x200). (C) Positive expression in poorly differentiated carcinoma (magnification, x200). (D) Negative expression in poorly differentiated carcinoma (magnification, x200). (E) Negative expression in signet ring cell carcinoma (magnification, x200).

differentiated carcinoma and 7 of SRCC). Lymphatic invasion was positive in 41 cases and negative in 16, venous invasion was positive in 36 cases and negative in 21, and lymph node metastasis was positive in 22 cases. As regards the depth of invasion, T1a was detected in 6 cases, T1b in 18, T2 in 7, T3 in 14, T4a in 11 and T4b in 1 case. As regards disease stage, 26 cases were stage I, 5 were stage IIA, 9 were stage IIB, 16 were stage III and 1 was stage IVA.

PPAR-α expression in gastric carcinoma. The expression of PPAR-α was mainly localized to the nucleus and was present in all normal epithelial tissues (Fig. 1A). In terms of PPAR-α expression and clinicopathological factors, it was expressed in all cases of differentiated carcinoma (30/30, 100%; Fig. 1B), while positive and negative expression was observed in cases of undifferentiated carcinoma (14/27, 51.9%). In terms of PPAR-α expression and histological subtype, PPAR-α expression was significantly higher in differentiated carcinoma compared with undifferentiated carcinoma ($P<0.01$; Table II). Undifferentiated carcinoma included poorly differentiated carcinoma and SRCC, and PPAR-α expression differed significantly between poorly differentiated carcinoma (both positive and negative: 14/20, 70%; Fig. 1C and D) and SRCC (not expressed: 0/7, 0%; Fig. 1E and Table III; $P<0.01$). PPAR-α expression was not significantly affected by sex, age, lymphatic invasion, venous invasion, lymph node metastasis, depth of invasion or stage (Table II).

Table II. Relationship between PPAR-α expression and clinicopathological parameters of gastric carcinoma.

Parameters	Number of cases	PPAR-α expression (-)	PPAR-α expression (+)	P-value
Sex				0.082
Male	42	7	35	
Female	15	6	9	
Age, years				0.172
<72	27	4	23	
≥72	30	9	21	
Histological type				<0.010[a]
Differentiated carcinoma	30	0	30	
Undifferentiated carcinoma	27	13	14	
Lymphatic invasion				>0.999
Positive	41	9	32	
Negative	16	4	12	
Venous invasion				>0.999
Positive	36	8	28	
Negative	21	5	16	
Lymph node metastasis				0.199
Positive	22	7	15	
Negative	35	6	29	
Depth of invasion				0.322
T1a	6	0	6	
T1b	18	5	13	
T2	7	1	6	
T3	14	3	11	
T4a	11	3	8	
T4b	1	1	0	
Stage				0.279
I	26	4	22	
IIA	5	2	3	
IIB	9	2	7	
III	16	4	12	
IVA	1	1	0	

[a]P<0.05 was considered to indicate statistically significant differences (Pearson's χ^2 test). PPAR-α, peroxisome proliferator-activated receptor-α.

Discussion

In the present study, the expression of PPAR-α was investigated in 57 patients with gastric carcinoma. Immunohistochemical staining was performed using an HRP-labeled monoclonal anti-PPAR-α antibody to elucidate the relationship between changes in PPAR-α expression and clinicopathological factors. PPAR-α expression was found to be correlated with histological type, with significantly higher expression levels observed in differentiated carcinoma and lower expression levels in undifferentiated carcinoma. These results provide evidence for the development of useful molecular markers that may predict cancer progression and outcome in patients with gastric carcinoma, as PPAR-α expression was shown to be downregulated in undifferentiated gastric carcinoma.

Gastric carcinoma is generally subdivided into differentiated and undifferentiated types, with the latter mainly including poorly differentiated carcinoma and SRCC, as defined by the Japan Gastric Cancer Classification (21). Patients with SRCC have a higher stage of progression and poorer prognosis compared with those with other types of gastric carcinoma (22,23), and poorly differentiated carcinoma has been associated with lymph node metastasis, which carries a poor prognosis (24-26). Poorly differentiated carcinoma and SRCC are generally considered to have a poor prognosis and high malignant potential (27). Therefore, it is crucial to detect undifferentiated carcinomas at an early stage and develop new markers for histological subtypes.

The activation of PPAR-α is widely known to induce cell metabolism, inflammation, differentiation, cell cycle arrest

Table III. Association between undifferentiated gastric carcinoma types and PPAR-α expression.

Histological type	Number of cases	PPAR-α expression (-)	PPAR-α expression (+)	P-value
Poorly differentiated carcinoma	20	6	14	<0.010[a]
Signet ring cell carcinoma	7	7	0	

[a]P<0.05 was considered to indicate statistically significant differences (Fisher's exact test). PPAR-α, peroxisome proliferator-activated receptor-α.

and apoptosis in ovarian cancer (11), hepatocellular carcinoma (28-30), colorectal carcinoma (31,32) and endometrial cancer (33). Furthermore, regarding the levels of PPAR-α expression in cancer tissue, immunohistochemistry revealed that PPAR-α expression levels were significantly low in clear cell renal cell carcinoma specimens and were correlated with patient age and sex, and cancer stage and grade (34). Although several studies have examined the relationship between PPAR-α expression and cancer outcomes (32-34), there is currently no information on the association between PPAR-α expression and clinicopathological factors in poorly differentiated carcinoma and SRCC. The association between PPAR-α and gastric cancer was also analyzed by cBioPortal (https://www.cbioportal.org), and the findings obtained revealed that limited information is currently available on PPAR-α and gastric cancer (data not shown). The results of the present study demonstrated that PPAR-α expression was downregulated in highly malignant undifferentiated carcinoma, suggesting that its expression may serve a role in the degree of differentiation in gastric carcinoma.

Undifferentiated carcinoma included poorly differentiated carcinoma and SRCC in the present study. Therefore, it was investigated whether PPAR-α expression differed between poorly differentiated carcinoma and SRCC. A comparison between poorly differentiated carcinoma and SRCC revealed that PPAR-α expression was absent in SRCC (0/7, 0%), but present in poorly differentiated carcinoma (14/20, 70%), and the difference was statistically significant (P<0.01). As regards the expression of PPAR-α and histology, no comparative study has been conducted to date on the associations of PPAR-α expression with poorly differentiated carcinoma and SRCC. However, PPAR-γ, a subtype of PPARs, has been examined in relation to histological types (35,36). Immunohistochemical staining for PPAR-γ in gastric cancer tissues revealed that the frequency of positive samples decreased as cancer transitioned from differentiated to poorly differentiated carcinoma, and a gradual decrease in PPAR-γ activity was found to contribute to the histological differentiation of gastric cancer cells and tumor progression (35). Furthermore, the majority of SRCC samples lacked expression of PPAR-γ (37). These findings prompted us to investigate whether PPAR-α expression is also lower in undifferentiated compared with that in differentiated cancers. The finding of the differential expression of PPAR-α in poorly differentiated carcinoma and SRCC suggests similarities between PPAR-α and PPAR-γ. Although PPAR-α has been shown to regulate lipid energy metabolism, cancer cell differentiation and apoptosis (38), its relationship with differentiation, namely poorly differentiated carcinoma and SRCC, remains unclear and requires further study.

In the present study, no significant differences were observed in the expression of PPAR-α between normal epithelial tissues and differentiated carcinomas, whereas its expression was lower in the two undifferentiated, more malignant types compared with that in the differentiated type. Since the relationship between PPAR-α expression and histology has not yet been elucidated in detail, further studies with a larger number of subjects are needed to clarify the relationship between PPAR-α expression and tumor progression and to analyze long-term clinical survival. The relationship between PPAR-α and patient prognosis was not assessed in this cohort as the hospital did not have post-treatment data on the patients examined in the present study. Furthermore, no cytology materials were available and, thus, additional experiments could not be conducted. The findings of molecular biological studies using cultured cells will be discussed in future studies. In conclusion, the findings of the present study demonstrated that the downregulated expression of PPAR-α may be involved in the biological transformation of tumors, suggesting that PPAR-α is an important protein associated with tumor histology and may hold potential as a prognostic marker.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

TMo and EH designed the study. TMo, YT, KK and SK performed the experiments. TMa and EI collected the pathological data. TMo, YT and EH analyzed all data. TMo, YT and EH wrote the manuscript. TMo, YT, ST, HO and EH critically

reviewed the manuscript for important intellectual content. TAM, YT and EH confirm the authenticity of the raw data. All the authors have read and approved the final manuscript.

Ethics approval and consent to participate

All clinical samples were provided after obtaining written informed consent from the patients. The present study was conducted with the approval of the Institutional Research Ethics Committee of the Kagawa Prefectural University of Health Sciences (Kagawa, Japan; approval no. 215).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Kepil N, Batur S and Goksel S: Immunohistochemical and genetic features of mucinous and signet-ring cell carcinomas of the stomach, colon and rectum: A comparative study. Int J Clin Exp Pathol 12: 3483-3491, 2019.
2. Katada T, Ishiguro H, Kuwabara Y, Kimura M, Mitui A, Mori Y, Ogawa R, Harata K and Fujii Y: microRNA expression profile in undifferentiated gastric cancer. Int J Oncol 34: 537-542, 2009.
3. Adachi Y, Yasuda K, Inomata M, Sato K, Shiraishi N and Kitano S: Pathology and prognosis of gastric carcinoma: Well versus poorly differentiated type. Cancer 89: 1418-1424, 2000.
4. Noda S, Soejima K and Inokuchi K: Clinicopathological analysis of the intestinal type and diffuse type of gastric carcinoma. Jpn J Surg 10: 277-283, 1980.
5. Henson DE, Dittus C, Younes M, Nguyen H and Albores-Saavedra J: Differential trends in the intestinal and diffuse types of gastric carcinoma in the United States, 1973-2000: Increase in the signet ring cell type. Arch Pathol Lab Med 128: 765-770, 2004.
6. Nakamura T, Yao T, Niho Y and Tsuneyoshi M: A clinicopathological study in young patients with gastric carcinoma. J Surg Oncol 71: 214-219, 1999.
7. Pozos-Ochoa LI, Lino-Silva LS, León-Takahashi AM and Salcedo-Hernández RA: Prognosis of signet ring cell carcinoma of the colon and rectum and their distinction of mucinous adenocarcinoma with signet ring cells. A comparative study. Pathol Oncol Res 24: 609-616, 2018.
8. Hyngstrom JR, Hu CY, Xing Y, You YN, Feig BW, Skibber JM, Rodriguez-Bigas MA, Cormier JN and Chang GJ: Clinicopathology and outcomes for mucinous and signet ring colorectal adenocarcinoma: Analysis from the national cancer data base. Ann Surg Oncol 19: 2814-2821, 2012.
9. Nolte RT, Wisely GB, Westin S, Cobb JE, Lambert MH, Kurokawa R, Rosenfeld MG, Willson TM, Glass CK and Milburn MV: Ligand binding and co-activator assembly of the peroxisome proliferator-activated receptor-gamma. Nature 395: 137-143, 1998.
10. Pozzi A, Ibanez MR, Gatica AE, Yang S, Wei S, Mei S, Falck JR and Capdevila JH: Peroxisomal proliferator-activated receptor-alpha-dependent inhibition of endothelial cell proliferation and tumorigenesis. J Biol Chem 282: 17685-17695, 2007.
11. Yokoyama Y, Xin B, Shigeto T, Umemoto M, Kasai-Sakamoto A, Futagami M, Tsuchida S, Al-Mulla F and Mizunuma H: Clofibric acid, a peroxisome proliferator-activated receptor alpha ligand, inhibits growth of human ovarian cancer. Mol Cancer Ther 6: 1379-1386, 2007.
12. Ramanan S, Kooshki M, Zhao W, Hsu FC and Robbins ME: PPARalpha ligands inhibit radiation-induced microglial inflammatory responses by negatively regulating NF-kappaB and AP-1 pathways. Free Radic Biol Med 45: 1695-1704, 2008.
13. Wang CY, Chao YJ, Chen YL, Wang TW, Phan NN, Hsu HP, Shan YS and Lai MD: Upregulation of peroxisome proliferator-activated receptor-α and the lipid metabolism pathway promotes carcinogenesis of ampullary cancer. Int J Med Sci 18: 256-269, 2021.
14. Grygiel-Górniak B: Peroxisome proliferator-activated receptors and their ligands: Nutritional and clinical implications-a review. Nutr J 13: 17, 2014.
15. Pandey MK, Gupta SC, Nabavizadeh A and Aggarwal BB: Regulation of cell signaling pathways by dietary agents for cancer prevention and treatment. Semin Cancer Biol 46: 158-181, 2017.
16. Liu YL, Lin LC, Tung YT, Ho ST, Chen YL, Lin CC and Wu JH: *Rhododendron oldhamii* leaf extract improves fatty liver syndrome by increasing lipid oxidation and decreasing the lipogenesis pathway in mice. Int J Med Sci 14: 862-870, 2017.
17. Kliewer SA, Forman BM, Blumberg B, Ong ES, Borgmeyer U, Mangelsdorf DJ, Umesono K and Evans RM: Differential expression and activation of a family of murine peroxisome proliferator-activated receptors. Proc Natl Acad Sci USA 91: 7355-7359, 1994.
18. Japanese Gastric Cancer Association: Japanese Classification of Gastric Carcinoma. 15th ed. Tokyo, Kanehara Shuppan, 2017 (In Japanese).
19. Tokuhara Y, Morinishi T, Matsunaga T, Ohsaki H, Kushida Y, Haba R and Hirakawa E: Claudin-1, but not claudin-4, exhibits differential expression patterns between well- to moderately-differentiated and poorly-differentiated gastric adenocarcinoma. Oncol Lett 10: 93-98, 2015.
20. Lin MS, Huang JX, Chen WC, Zhang BF, Fang J, Zhou Q, Hu Y and Gao HJ: Expression of PPARγ and PTEN in human colorectal cancer: An immunohistochemical study using tissue microarray methodology. Oncol Lett 2: 1219-1224, 2011.
21. Dicken BJ, Bigam DL, Cass C, Mackey JR, Joy AA and Hamilton SM: Gastric adenocarcinoma: Review and considerations for future directions. Ann Surg 241: 27-39, 2005.
22. Liu X, Cai H, Sheng W, Yu L, Long Z, Shi Y and Wang Y: Clinicopathological characteristics and survival outcomes of primary signet ring cell carcinoma in the stomach: Retrospective analysis of single center database. PLoS One 10: e0144420, 2015.
23. Pernot S, Voron T, Perkins G, Lagorce-Pages C, Berger A and Taieb J: Signet-ring cell carcinoma of the stomach: Impact on prognosis and specific therapeutic challenge. World J Gastroenterol 21: 11428-11438, 2015.
24. Jinawath N, Furukawa Y, Hasegawa S, Li M, Tsunoda T, Satoh S, Yamaguchi T, Imamura H, Inoue M, Shiozaki H and Nakamura Y: Comparison of gene-expression profiles between diffuse- and intestinal-type gastric cancers using a genome-wide cDNA microarray. Oncogene 23: 6830-6844, 2004.
25. Sipponen P: Gastric cancer: Pathogenesis, risks, and prevention. J Gastroenterol 37 (Suppl 13): S39-S44, 2002.
26. Hwang CS, Ahn S, Lee BE, Lee SJ, Kim A, Choi CI, Kim DH, Jeon TY, Kim GH, Song GA and Park DY: Risk of lymph node metastasis in mixed-type early gastric cancer determined by the extent of the poorly differentiated component. World J Gastroenterol 22: 4020-4026, 2016.
27. Chirieac LR, Swisher SG, Correa AM, Ajani JA, Komaki RR, Rashid A, Hamilton SR and Wu TT: Signet-ring cell or mucinous histology after preoperative chemoradiation and survival in patients with esophageal or esophagogastric junction adenocarcinoma. Clin Cancer Res 11: 2229-2236, 2005.
28. Maggiora M, Oraldi M, Muzio G and Canuto RA: Involvement of PPARα and PPARγ in apoptosis and proliferation of human hepatocarcinoma HepG2 cells. Cell Biochem Funct 28: 571-577, 2010.
29. Zhang N, Chu ES, Zhang J, Li X, Liang Q, Chen J, Chen M, Teoh N, Farrell G, Sung JJ and Yu J: Peroxisome proliferator activated receptor alpha inhibits hepatocarcinogenesis through mediating NF-κB signaling pathway. Oncotarget 5: 8330-8340, 2014.
30. You BJ, Hour MJ, Chen LY, Luo SC, Hsu PH and Lee HZ: Fenofibrate induces human hepatoma Hep3B cells apoptosis and necroptosis through inhibition of thioesterase domain of fatty acid synthase. Sci Rep 9: 3306, 2019.
31. Gao J, Liu Q, Xu Y, Gong X, Zhang R, Zhou C, Su Z, Jin J, Shi H, Shi J and Hou Y: PPARα induces cell apoptosis by destructing Bcl2. Oncotarget 6: 44635-44642, 2015.
32. Morinishi T, Tokuhara Y, Ohsaki H, Ibuki E, Kadota K and Hirakawa E: Activation and expression of peroxisome proliferator-activated receptor alpha are associated with tumorigenesis in colorectal carcinoma. PPAR Res 2019: 7486727, 2019.

33. Knapp P, Chabowski A, Błachnio-Zabielska A, Jarząbek K and Wołczyński S: Altered peroxisome-proliferator activated receptors expression in human endometrial cancer. PPAR Res 2012: 471524, 2012.
34. Luo Y, Chen L, Wang G, Qian G, Liu X, Xiao Y, Wang X and Qian K: PPARα gene is a diagnostic and prognostic biomarker in clear cell renal cell carcinoma by integrated bioinformatics analysis. J Cancer 10: 2319-2331, 2019.
35. Yu H and Xin Y: Down-regulated expressions of PPARγ and its coactivator PGC-1 are related to gastric carcinogenesis and Lauren's classification in gastric carcinoma. Chin J Cancer Res 25: 704-714, 2013.
36. Theocharis S, Kanelli H, Politi E, Margeli A, Karkandaris C, Philippides T and Koutselinis A: Expression of peroxisome proliferator activated receptor-gamma in non-small cell lung carcinoma: Correlation with histological type and grade. Lung Cancer 36: 249-255, 2002.
37. Nomura S, Nakajima A, Ishimine S, Matsuhashi N, Kadowaki T and Kaminishi M: Differential expression of peroxisome proliferator-activated receptor in histologically different human gastric cancer tissues. J Exp Clin Cancer Res 25: 443-448, 2006.
38. Tan Y, Wang M, Yang K, Chi T, Liao Z and Wei P: PPAR-α modulators as current and potential cancer treatments. Front Oncol 11: 599995, 2021.