Adipose Tissue-Released Hormone Adiponectin: A Review of its Anti-Neoplastic Effects

Niki Nourmohammadi, Emily Converse, Michaela LeDonne, Pranav Cannanbilla, Johnny Dang, Dario Fiorelli, Connor Foote, Tanner Foster, Aaron Grossberg, Kelsie Hendrick, Camilla Herbin, Marcel Mio, Minh Nguyen, Kevin Pak, Alexander Pappas, James Pirraglia, Allison Quirk, John Sinclair, Daniel Borsch, Amitabha Ray

Lake Erie College of Osteopathic Medicine- Seton Hill, Greensburg, PA

Introduction and Methods

Adiponectin is a hormone-like cytokine (or adipokine) mainly secreted from fat cells. Adiponectin has anti-inflammatory properties and inversely correlates with body fat mass including visceral adiposity. This cytokine is present in different isoforms and suggested to mediate its biological functions mainly through AdipoR1 and AdipoR2 receptors. Low adiponectin levels have been associated with diabetes, heart disease and cancer. To better understand the role of adiponectin in various cancers, we performed a review of PubMed literature. A targeted search with keywords "adiponectin" + respective cancer of interest yielded a total of 1322 human, animal, and cell- line research study articles. For human and animal studies, only clinical and epidemiological articles examining aggressiveness of primary tumor and patient outcome serum in relation to serum levels of adiponectin were chosen for review. For *in vitro* cell- line studies, only articles examining the effect of adiponectin on tumor cell proliferation or tumor cell signaling were chosen for review. All previous review articles were filtered from our survey. The final total of articles eligible for our review was 191 (Table 1).

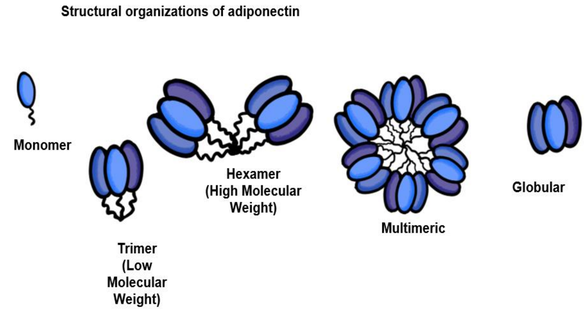

Figure 1. Adiponectin structure

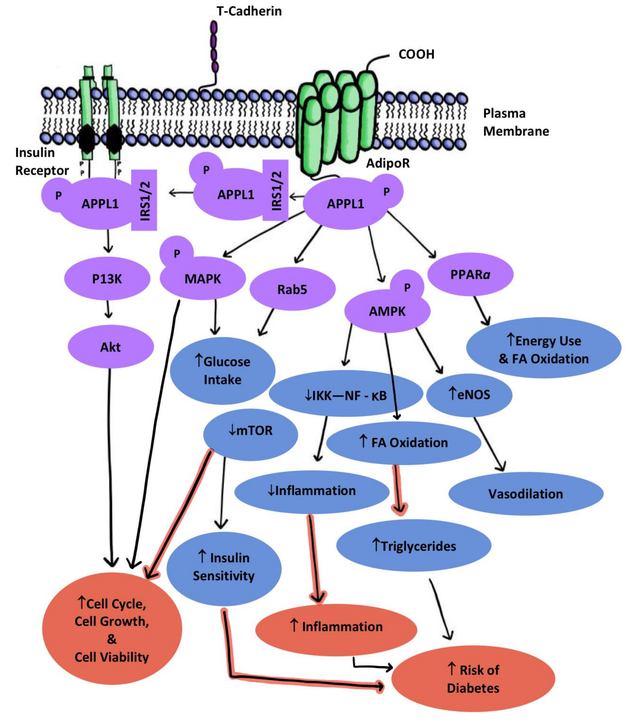

Figure 2. Adiponectin signaling cascade

Akt: a serine/threonine kinase or protein kinase B, **AMPK**: adenosine monophosphate-activated protein kinase, **APPL1**: adaptor protein, adiponectin receptor binding protein, **eNOS**: endothelial nitric oxide synthase, **FA:** fatty acid, **IKK**: inhibitor of nuclear factor-kB kinase complex, **NF-κB**: nuclear factor kappa-light-chain-enhancer of activated B cells, **IRS1/2**: Insulin receptor substrate 1 and 2, **MAPK:** mitogen-activated protein kinase, **mTOR**: mechanistic target of rapamycin, **P**: phosphorylation, **PPARα**: peroxisome proliferator-activated receptor alpha, **P13K**: Phosphoinositide 3-kinases, also called phosphatidylinositol 3-kinases, **Rab5**: a small GTPase (GTP: guanosine-5'-triphosphate)

Breast Cancer

Fourteen studies looking at adiponectin levels and their correlation with breast cancer risk found that serum adiponectin was inversely related to risk of breast cancer [1-14]. Serum adiponectin levels were also inversely related to tumor adiponectin levels in breast cancer patients [5]. Three studies found that adiponectin levels increased with breast cancer risk [15-17]. Six studies found that there was no significant difference between adiponectin levels in breast cancer patients and control groups [18-23].

Animal studies reviewed also agree that adiponectin plays a protective role in breast cancer. Of the eight animal studies that examined the correlation between adiponectin levels and cancer, seven studies found that low adiponectin levels were correlated to increased cancer formation and just one showed the opposite [24-31].

A review of cell culture studies showed that, at higher levels of adiponectin, genes that are considered pro-apoptotic are stimulated and anti-apoptotic genes are inhibited [32]. Specifically, apoptotic rates are increased in MDA-MB 231, MCF-7 and SK-BR-3 cell lines [33]. Adiponectin can also inhibit endothelial cell proliferation by 15% and migration by 82% [34]. Globular adiponectin has been shown to have positive effects on breast cancer patients by decreasing the cell number of MCF-7 cells with an increase in the number of cells in G0/G1 phase, decreasing the number of cells in S phase and increasing caspase-3 activity [35-36].

Ovarian and Endometrial Cancer

For human, animal, and cell line studies examining the correlation between endometrial cancer and adiponectin levels, the majority revealed decreased adiponectin levels in the presence of endometrial cancer [37-61].
Among the human, animal, and cell studies investigating the relationship between adiponectin levels and ovarian cancer, a consistent trend was not identified [62-67]. For both ovarian and endometrial cancers, there was a limited number of studies performed investigating the cancers' relationship with adiponectin levels.

Prostate Cancer

The data show that low levels of adiponectin were associated with higher Gleason scores [68-85].The Gleason score is a grading system to assess how much of the biopsy is healthy tissues and how much is indicative of cancer, with the higher the score equating to a higher risk of prostate cancer. However, other studies observed that adiponectin levels were not a reliable diagnostic or screening tool for prostate cancer [86-95]. It was also found that peri-prostatic white adipose tissue inflammation might be connected with lower adiponectin levels and more aggressive cancers [77, 84].

Thyroid Cancer

Among human studies, elevated adiponectin levels were found to have a negative association with differentiated thyroid cancer compared to benign thyroid disease [96-99]. However, other results of another human study indicated that adiponectin had no significant association with papillary thyroid cancer and medullary thyroid cancer [101-102]. Among cell line studies, over-expression of adiponectin receptors was observed in some tissues of papillary thyroid cancer [103].

Colon Cancer

For colon cancer, three human studies found higher levels of adiponectin to be protective against cancer [104-107], whereas one associated high levels of adiponectin with cancer promotion [107]. No association has also been suggested [108].

Animals studies also suggest high levels of adiponectin are protective against cancer [109-111]. This observation is agreed with by five cellular studies [112-116]. One reviewed cellular study suggested adiponectin promoted cancer [117].

Liver Cancer

The role of adiponectin in human hepatic cancers appears to be complex. Indeed, some studies have suggested higher circulating levels of adiponectin were protective against hepatocellular carcinoma (HCC) in patients with liver cirrhosis [118-120]. Lower levels of adiponectin have also been found to be associated with worse histological grades of HCC tumor [121]. Other studies, however, suggest that high levels of adiponectin are associated with an increased risk of developing HCC [122-129], or worse outcomes in HCC patients [129-130].

In vivo studies have associated low levels of adiponectin with the development of HCC [130-131]. Adiponectin has also been found to prevent tumor metastasis in a mouse model by suppressing angiogenesis [132]. In vitro studies have suggested that adiponectin inhibits leptin mediated proliferation of HCC [133]. Adiponectin has also been shown to be protective by promoting apoptosis[134-135].

Pancreatic Cancer

The four human trials that investigated pre-diagnostic adiponectin levels found an association between high adiponectin levels and a decreased risk of pancreatic cancer [136-140]. In contrast, 3 research articles that examined post-diagnostic adiponectin levels showed adiponectin levels were elevated in pancreatic tumor cases compared to control groups [141-143].

Overall the animals studies had contradicting results, with two demonstrating adiponectin decreased pancreatic tumor size [144], while another study suggested adiponectin was correlated with an increase in pancreatic tumor size [145]. One study found specifically that adiponectin contributes to pancreatic tumor growth by inhibiting apoptosis [146]. Among limited cell culture studies, one available study suggested that adiponectin was capable of inducing apoptosis and the receptors for adiponectin were minimally expressed in pancreatic cancer cell-lines [147-148].

Table 1. Review of adiponectin and its anti-neoplastic effects by system

Cancer site	Human studies	Animal studies	Cell line studies
Breast	15 | 3 | 6	7 | 1 | 0	0 | 4 | 0
Endometrium	15 | 0 | 2	0 | 0 | 0	6 | 0 | 0
Ovary	2 | 0 | 1	1 | 0 | 1	1 | 0 | 0
Prostate	9 | 4 | 6	—	9 | 0 | 0
Thyroid	2 | 1 | 2	—	1 | 1 | 0
Colorectal	3 | 1 | 1	3 | 0 | 0	5 | 1 | 0
Liver	9 | 3 | 0	3 | 0 | 0	3 | 0 | 0
Pancreas	Pre-Dx: 4 | 0 | 0 Post-Dx: 0 | 3 | 1	1 | 2 | 1	3 | 0 | 0
Renal	12 | 1 | 0	—	1 | 0 | 0
Lung	6 | 0 | 2	0 | 0 | 0	4 | 0 | 0
Skin	0 | 0 | 1	1 | 0 | 0	2 | 0 | 0
Leukemia	9 | 0 | 0	—	—
Lymphoma	0 | 5 | 0	—	—

KEY
Blue = negative correlation between adiponectin and cancer
Red = positive correlation between adiponectin and cancer
Green = no correlation

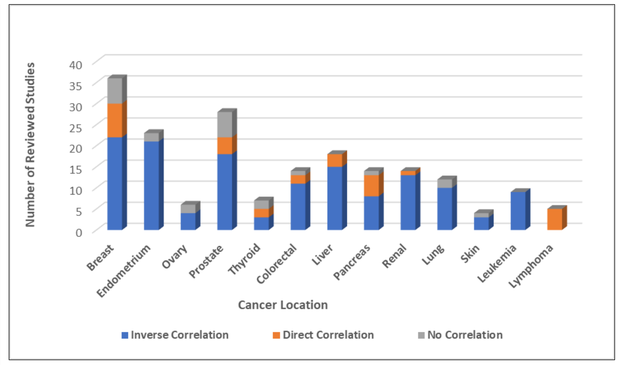

Figure 3. Summary of adiponectin and its anti-neoplastic effects by system
In this bar graph figure, the blue indicates the number of articles reporting a negative relationship between adiponectin levels, and the organ system related cancer. The orange indicates a positive relationship between adiponectin levels and the organ system related cancer and the grey was the number of articles that did not observe a correlation. Exact numerical values listed in table 1 to the left.

Renal Cancer

Decreased serum adiponectin levels were associated with an increased risk of renal cell carcinoma and/or an increased risk of metastasis [149-160]. One paper found a direct significant correlation of adiponectin with renal cell carcinoma in African Americans and females and a non-significant correlation of adiponectin in Caucasian males [161].

Lung Cancer

Current evidence fails to reveal any prognostic/diagnostic values of adiponectin serum level in association with lung carcinoma [162-163]. However, studies show adiponectin has an inhibitory effect on NSCLC cell proliferation in a time- and dose-dependent manner via apoptosis or cell cycle arrest by modulation of AdipoR1 and AdipoR2 [164-173].

Skin Cancer

Adiponectin was shown to be downregulated in keratoacanthoma, a variant of squamous cell carcinoma [174]. It was also found to be negatively correlated with insulin resistant induced melanoma [175]. In one study, high fat diets were shown to decrease plasma serum levels of adiponectin and increase inflammation in UV irradiated mice, resulting in a greater chance of the mice contracting skin cancer [176]. A single human study noted an inverse association of serum adiponectin with melanoma in Greece, but the significance was unclear [177].

Leukemia and Lymphoma

Epidemiological studies demonstrated that adiponectin levels showed an inverse correlation with incidence when measured in patients with leukemia [178-186]. Examination of lymphoma also suggested a positive correlation of serum adiponectin levels in patients diagnosed with lymphoma [187-191]. No *in vivo* animal or *in vitro* cellular study results regarding leukemia or lymphoma matched our survey criteria.

Discussion and Conclusion

Our review of PubMed articles based on the search criteria of "adiponectin + cancer" was inconclusive. While *in vivo* animal studies and *in vitro* studies generally observe an inverse relationship between cancer aggressiveness and adiponectin levels, suggesting a protective role, the relationship between adiponectin and cancer in humans appears to be much more complex. In liver cancer, a direct relationship was suggested, with higher levels of adiponectin being associated with a more aggressive cancer, and no association could be demonstrated in many other cancers. In some cancers, however, such as endometrial, colon, kidney, postmenopausal breast cancer, and leukemia, there appears to be an inverse protective relationship between adiponectin levels and cancer, suggesting potential for management of adiponectin as a treatment strategy at least in certain types of cancers. To maximally exploit the beneficial effects of adiponectin, it will be crucial to better understand its biological connection with other hormones, such as insulin, insulin-like growth factors, and leptin, and also the modulation of adiponectin and adiponectin receptor levels in pre-neoplastic and malignant states.

References

1.Akyol M, et al. Chemotherapy, 2016;61(2), 57.
2.Ahmed SDH, et al. Asian Pac. J. Cancer Prev. 2014;16(12), 4945.
3.Catsburg, C, et al. Cancer Res. 2014;74(12), 3248.
4.Chen DC, et al. Cancer Lett. 2006;237(1), 109.
5.Duggan C, et al. J Clin Oncol. 2011;29(1), 32.
6.Güven HE, et al. Eur J Breast Health. 2019;15(1), 13.
7.Hou WK, et al. Chin Med J. 2007;120(18), 1592.
8.Iyengar N, et al. Clin Cancer Res, 2016;22(9), 2288.
9.Körner A, et al. J Clin Endocrinol Metab. 2007;92(3), 1041.
10.Oh S, et al. Breast Cancer Res. 2011;13(2), R34.
11.Ozmen HK, et al. Open Med (Wars), 2017;12, 189.
12.Pasha HF, et al. J Gene Med. 2019;21(10), e3120.
13.Shahar S, et al. Asian Pac. J. Cancer Prev. 2010;11(1), 61.
14.Sonmez B, et al. J BUON. 2011;16(2), 227.
15.Al Awadhi S, et al. Indian J Med Res. 2012;135(4), 500.
16.Jeong Y, et al. J Breast Cancer. 2011;14(2), 96.
17.Karaduman M. et al. Med Oncol. 2007;24(4), 361.
18.Coskun T, et al. Mol Clin Oncol. 2016;4(5), 893.
19.Cubukcu E, et al. Contemp Oncol. 2014;18(1), 34.
20.Guo M, et al. PLoS One, 2015; 10(6). doi.org/10.1371/journal.pone.0129246.
21.Kang J, et al. J Korean Med Sci. 2007;22(1), 117.
22.Patrício M, et al. BMC Cancer. 2018;18(1), 29.
23.Sambiasi D, et al. Oncotarget, 2017;8(60), 101255.
24.Dogan S, et al. Oncol Lett. 2010;1(1), 167.
25.Ecker BL, et al. Breast Cancer Res. 2019; 21(1).
26.Lam JB, et al. PLoS ONE, 2009;4(3). doi: 10.1371/journal.pone.0004968
27.Lamas B, et al. Mol Carcinog. 2013; 54(1), 58.
28.Liu J, et al. Oncotarget. 2013;4(10).
29.Nachat-Kappes, R. et al. PLoS One. 2012;7(12). doi:10.1371/journal.pone.005152.
30.Theriau CF, et al. PLoS One, 2017;12(9). doi: 10.1371/journal.pone.0183897.
31.Denzel MS, et al. Clin Cancer Res. 2009;15(10), 3256–3264.
32.Dos Santos, E. et al (1994). Oncol Rep, 1994;20(4), 971.
33.Pfeiler G, et al. Oncol Rep. 2008;787.
34.Dubois V, et al. PLoS One, 2013; 8(3). doi: 10.1371/journal.pone.0058541
35.Nepal S, & Park, PH. (2014). Biomol Ther, 2014; 22(5), 384.
36.Shrestha A, et al.. J Cell Physiol. 2015;231(2), 357–369.
37.Aminimoghaddam S, et al. Pathol Res Pract. 2015;211(4):293.
38.Ashizawa N, et al. Gynecol Oncol. 2010;119(1):65.
39.Bohlouli S, et al. Int J Fertil Steril. 2013;7(1):43.
40.Busch EL, et al. Horm Cancer. 2018;9(1):33.
41.Ciortea R, et al. 2018;59(5):1165.
42.Cong L, et al. Endocr-Relat Cancer. 2007;14(3):713.
43.Cust AE, et al. J Clin Endocr Metab. 2007;92(1):255.
44.Dallal CM, et al. Endocr-Relat Cancer. 2012;20(1):151.
45.Dossus LE, et al. Am. J. Epidemiol. 2013;177(8):787.
46.Haggerty AF, et al. Gynecol Oncol. 2016;140(2):239.
47.Luhn P, et al. Cancer Epidemiol Biomarkers Prev. 2013;22(7):1304.
48.Ma Y, et al. J Gynecol Oncol. 2013;24(4):336.
49.Maso LD, et al. J Clin Endocr Metab. 2004;89(3):1160.1
50. Mccampbell, A, et al. Curr Mol Med. 2016;16(3):252.
51. Modesitt SC, et al. Gynecol Oncol. 2012;124(3):431.
52.Moon H-S, et al. Mol Cancer Ther. 2011;10(12):2234
53.Ohbuchi, Y, et al. Int Journal of Clinical Oncology. 2013;19(4):667-673.
54.Petridou E, et al. J Clin Endocr Metab. 2003;88(3):993.
55.Shang CG, et al. Chin Med J . 2017;130(15):1831.
56.Soliman PT, et al. Cancer. 2006;106(11):2376.
57.Uzan J, et al. Int J Mol Sci . 2017;18(5):1055.
58.Wang Z, et al. Int J Gynecol Obstet. 2019;145(1):34
59.Yabushita H, et al. Oncol Lett.. 2014;7(4):1109.
60.Yamauchi N, et al. Int J Gynecol Pathol. 2012;31(4):352.
61.Zhang L, et al. Gynecol Oncol. 2015;137(2):311
62.Hoffmann M, et al. Horm Cancer. 2018; 9(3): 166
63.Jin JH, et al. Obstet Gynecol Sci. 2016; 59(4): 279
64.Li X, et al. Med Sci Monit. 2017; 23: 1514
64.Li X, et al. Med Sci Monit. 2017; 23: 1514
65.Otokozawa S, et al. Asian Pac. J. Cancer Prev. 2015; 16(12): 4987
66.Słomian GJ, et al. Endokrynol Pol. 2019; 70(1): 57
67.Tiwar A, et al. Int J Gynecol Cancer. 2015;25(3): 399
68.Li H, et al. Clin Chem. 2010;56(1):34
69.Goktas S, et al. Urology. 2005;65:1168
70.JD, Miyazaki T., et al. Biochem Biophys Res Commun. 2006; 340:1158
71.Mistry T, et al. BJU Int. 2008;101:1317
72.Grossmann ME, et al. Oncol Res. (2009) 18:269
73.Zakikhani M, et al. Cancer Prev Res. 2008;1(5):369
74.Arisan ED, et al. Urol. Int. 2009;82:203
75.Grosman H, et al. Aging Male. 2010;13:87
76.Lu JP, et al. Prostate Cancer Prostatic Dis. 2012;15:28
77.Ribeiro RJ, et al. Cell Physiol Biochem. 2012; 29(1–2):233
78.Burton A, et al. Cancer Causes Control. 2013; 24:323
79.Tewari R, et al. Cytokine. 2013;63:130
80.Gao Q, et al. Tumor Biol. 2015;36:4287
81.Gao Q, et al. Cell Biochem Biophys. 2014;70:461
82.Tan W, et al. Prostate. 2015;75:1197
83.Zhang Q, et al. Cytokine. 2016;85:148
84.Gucalp A, et al. Prostate Cancer Prostatic Dis. 2017;20(4):418
85.Kang M, et al. World J Mens Health. 2018;36(1):57
86.Nishimura K, et al. Minerva Urol Nefrol. 2012;64:199
87.Medina EA, et al. Cancer Epidemiol Biomarkers Prev. 2014;23(2):309
88.Housa D, et al. Physiol Res. 2008;57(3):451
89.Skeda A, et al. Prostate Int. 2015;3(3):87
90.Serretta V, et al. Urol Ann. 2018;10(3):280
91.Siemińska L, et al. Endokrynol Pol. 2018; 69:120
92.Stevens VL, et al. Cancer Epidemiol Biomarkers Prev. 2014;23:890.
93.Sher DJ, et al. Prostate. 2008;68:1592
94.Baillargeon J, et al. Cancer Epidemiol Biomarkers Prev. 2006;15:1331
95.Freedland SJ, et al. J Urol. 2005;174:126
96.Mele C, et al. Endocr Connect. 2019; 8 (7) 997
97.Lin SY, et al. Metabolism. 2010;59:195.
98.Dossus L, et al. Int J Cancer. 2018; 142 (7): 1332
99.Mitsiades N, et al. J Clin Endocrinol Metab. 2011;96(12):E2023-8.
100.Warakomski J, et al. Int J Endocrinol. 2018: 4921803
101.Abooshahab R, et al. Asian Pac J Cancer Prev. 2016; 17 (8): 3861
102.Pazaitou-Panayiotou K, et al. Endocr. Pract. 2016;22:68.
103.Cheng SP, et al. Cell Biochem Biophys 2013;65:203.
104.Saetang J, et al. Asian Pac J Cancer Prev. 2016;17:2119.
105.Tae CH, et al. BMC Cancer. 2014;14(1).
106.Song M, et al. Cancer Prev Res. 2013;6:875
107.Zekri A, et al. Asian Pac. J. Cancer Prev. 2015;16:6923–6928.
108.Canhoroz M,et al. J Cancer Res and Ther. 2014;10(2).
109.Zhang Y, et al. Oncotarget. 2017;8(15).
110.Takahashi H., et al. J Gastroenterol Hepatol. 2013;28:41
111.Mutoh M, et al. Gastroenterology. 2011;140:2000.
112.Nigro E,et al. Mol. Cell. Biochem. 2018;448:125–135.
113.Moon HS, et al. Gut. 2012;62(4).
114.Sugiyama M, et al. Int J Oncol. 2009;34:339.
115.Kim AY, et al. Mol Endocrinol. 2010;24(7).
116.Fenton JI, Birmingham JM. Mol Carcinog. 2010;49(7).
117.Cai L, et al. Mol Carcinog. 2015;55:1796
118.Kotani K, et al. Asian Pac J Cancer Prev. 2009; 10 Suppl:87-90.
119.Radwan HA, et al.Asian Pac J Cancer Prev. 2019;20(6):1833-1839.
120. Hamdy K, et al. J Endocrinol Invest. 2015;38(11):1225-31.
121.Sumie S, et al. PLoS One. 2011;6(11):e26840.
122.Chen MJ, et al. J Surg Oncol. 2012;106(2):181-7.
123.Sadik NA, et al. Hum Exp Toxicol. 2012;31(4):311-21.
124.Arano T, Nakagawa H, et al. Int J Cancer. 2011;129(9):2226-35.
125.Chen CL, et al. Cancer Epidemiol Biomarkers Prev. 2014;23(8):1659-71.
126.Michikawa T,et al. Cancer Epidemiol Biomarkers Prev. 2013;22(12):2250-7.
127.Aleksandrova K,et al. Hepatology. 2014;60(3):858–871.
128.Siegel AB,et al. Oncology. 2015;88(1):57–68.
129.Wang SN, et al. J Gastroenterol. 2014;49(9):1342-51.
130.Nishihara T, et al. World J Gastroenterol. 2008;14(42):6473–6480.
131.Kamada Y, Matsumoto H, et al. J Hepatol. 2007;47:556–564.
132.Man K, et al. Clin Cancer Res. 2010;16(3):967-77.
133.Sharma D,et al. Hepatology. 2010;52(5):1713–1722.
134.Xing SQ, et al. Biochem Pharmacol. 2015;93(2):221-31.
135.Saxena NK,et al. Gastroenterology. 2010;139(5):1762–1773.e17735.
136.Bao Y, et al. J Natl Cancer Inst. 2012;105(2), 95–103.
137.Grote VA,et al. International J Cancer. 2011;130(10), 2428–2437.
138.Krechler T, et al. Neoplasma, 2011;58(1), 58–64.
139.Stolzenberg-Solomon, RZ,et al. Am J Epidemiol. 2015;168(9), 1047.
140.Gasiorowska A, et al. Dig Dis Sci. 2015; 61(4), 1121–1129.
141.Dranka-Bojarowska D, et al. J Physiol Pharmacol. 2015;66(5), 653–663.
142.Chang MC, et al. Pancreas. 2007;35(1), 16–21.
143.Messaggio F, et al. Oncotarget, 2017;8(49).
144.White, PB, et al. J Gastrointest Surg. 2012;16(9), 1680–1685.
145.Zyromski N, et al. J Surg Res. 2009;151(2), 258–259.
146.Huang B, et al. Oncotarget. 2014;5(13), 4732–4745.
147.Akimoto M, et al. Cell Death Dis,.9(8).
148.Jiang J, et al. Int J Biol Sci. 15(2), 253–264.
149.F. Campo-Verde-Arbocco, et al. Oncotarget. 2017;8, 94223.
150.de Martino M, et al. Eur Urol Focus. 2016;2:197-203.
151.Liao LM, et al. Obesity (Silver Spring). 2013;21(7):1478–1485.
152.Zhang HP, et al. Oncol Lett 2017;13:463-8.
153.Wang H, et al. J Cancer 7:1340–1346.
154.Choi SH, et al. Urol Oncol 2016;34:259.e15-9.
155.Liao LM, et al. Carcinogenesis 2013;34:109-12.
156.Park JT,et al. Metabolism. 2011;60(1):121–6.10.
157.Horiguchi A,et al. Jpn J Clin Oncol 2008;38:106-11.
158.Spyridopoulos TN,et al. Int J Cancer. 2007;120:1573–8.
159.Pinthus JH, et al. Eur Urol 2008;54:866-73.
160.Liao LL, et al. Cancer Causes Control. 2017;28:801–807.
161.Liao LM, et al. Obesity (Silver Spring). 2013;21:1478–1485.
162.Boura P, et al. Lung Cancer Management. 2017;6(2):55-65.
163.Karapanagiotou EM, et al. Lung Cancer. 2008;61(3):391-7.
164.Cui E, et al. Oncol Rep. 2018;40(3):1330-1338.
165.Illiano M, et al. Pulm Pharmacol Therapy. 2017;45:114-120.
166.Nigro E, et al. Pulm Pharmacol Therapy. 2013;55:25-30.
167.Li Y et al. PLoS One. 2015;10(5):e0127751.
168.Su WM, et al. Int J Biol Markers. 2015;30(3):e286-93.
169.Nigro E, et al. Int. J Biochem Cell Biol. 2013;45(6):1145-53.
170.Kerenidi T.,et al. Med Oncol. 2013;30(2):507.
171.Abdul-Ghafar J, et al.Tohoku J of Exp Med. 2013;229(2):153-62.
172.Petridou ET, et al. Oncol. 2007;73(3-4):261-9.
173.Cui E, et al. Biochem Cell Biol. 2011;89(3):308-13.
174.Ra SH, et al. Mod Pathol. 2015;28(6):799-806.
175.Antoniadis AG, et al. Melanoma Res. 2011;21(6):541-6.
176.Meeran SM, et al. Toxicol Appl Pharmacol. 2009;241(3):303-10.
177.Mantzoros CS, et al. Eur J Cancer. 2007;43(9):1430-6.
178.Sun LY, et al. Mol Cancer, 2018;17(1), 127.
179.Petridou E, Mantzoros,et al. Br J Cancer, 2006;94(1), 156–160.
180.El-Baz HA, et al. Iran J Public Health/ 2013;42(5), 504–510.
181.Aref, S, et al., Hematol, 2013;18:4, 198-203.
182.Molica, S,et al. Adv Hematol, 2009;287974.
183.Molica, S, et al. Int J Hematol 2008;88, 374–380.
184.Avcu F, et al. Int J Hematol 83, 2006; 254–258.
185.Iversen PO, & Wiig, H. Clin Cancer Res, 2005;11(19), 6793–6799.
186.Han S, Jeong, et al. J Immunol, 2013;190(9), 4877–4886.
187.Petridou ET, et al. Pediatr. Blood Cancer, 2010;54: 311-315.
188.Senagolage MD, et al. Cell reports, 2016;25(12), 3283–3298.e6.
189.Riby, J, Mobley, J., et al. Prot Clin Appl, 2016;10: 1113-1121.
190.Conroy SM, et al. Cancer Epidemiol Biomarkers Prev, 2013;22(3), 337-347.
191.Han S, et al. J Immunol, 2013; 190(9), 4877–4886.