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Research Article

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When Anticancer Agents Are Applied to Adenocarcinoma Cells, Platelets Improve Their Survival Rate Medications: Mechanisms and Chemoresistance Implications

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ABSTRACT

Overview and Goals: Cancer cells are more likely to survive when they are not constrained by feedback control mechanisms. Chemosis and persistent side effects from chemotherapy might make cancer treatment more difficult to manage tumor cells' ability to survive. In this study, we looked at how platelets affect the survival and death of cancer cells treated with chemotherapy AN EXPERIMENTAL METHOD: Human adenocarcinoma cells, namely colonic (Caco-2) and ovarian (59 M) cells, were cultured for 1, 24, or 72 hours with or without platelets (1.5 · 108 mL-1). The drugs used were 5-fluorouracil (1–300 mg·mL–1) or paclitaxel (1–200 mg·mL–1). After incubation, cancer cells were isolated and used flow cytometry, Western blotting, real-time PCR, TaqMan® Gene Expression Assays, and proteomics to determine if the cells had survived or died ESSENTIAL OUTCOMES: Human platelets multiplied the ability of colonic and ovarian adenocarcinoma cells treated with 5-fluorouracil and paclitaxel, two common anticancer medications, to survive. Cancer cells expressed more cyclins, DNA repair proteins, and MAPKs when platelets were present. They also down- and up-regulated pro- and anti-apoptotic genes, increased the number of cells synthesizing DNA, and decreased the number in the quiescent phase. The thrombospondin-1, TGF-b, clustering, and chemokine RANTES were released, according to an investigation of the platelet-Caco-2 secretum. Lastly, thrombospondin-1 and human recombinant RANTES increased the ability of Caco-2 cells exposed to paclitaxel to survive SUMMARY AND IMPLICATIONS These findings show that platelets boost the survival, growth, and chemoresistance of adenocarcinoma cells to conventional anticancer medications. Changing the connections between cancer cells and platelets may be a fresh approach to raising the effectiveness of chemotherapy.

Keywords: Platelets, Adenocarcinoma Cells, Chemoresistance, Survival, Rantes, Thrombospondin-1

Introduction

The intricate process of platelet-cancer interactions involves the platelets interacting extensively with the cancer cells and microenvironment several stages of carcinogenesis, including the possibility of blood-borne metastases. When French physician Armand Trousseau discovered a significant rate of venous thrombosis in patients suffering from gastric carcinomas in 1865, it provided the first indication that vascular thrombosis and cancer were related. As epidemiological research revealed that two out of ten cancer patients may experience thrombotic problems during the clinical course of their disease, recent clinical and experimental evidence support the link between cancer and thrombosis [1]. Furthermore, stomach, ovarian, breast, and colon cancers have poor prognoses associated with thrombocytosis, which is frequently found in cancer patients [2,3]. Angiogenesis, invasion, survival in circulation, and metastasis are among the stages of cancer progression that platelets aid in [4,5].

Tumor cell-induced platelet aggregation (TCIPA) is one of the main processes underlying the interactions between platelets and cancer cells [6]. Platelet–cancer aggregates that form as a result of TCIPA stick to the endothelium and have the potential to distantly embolize the microvasculature. According to research, platelets engaged in cancer cell–platelet aggregates provide contractile force that disrupts these aggregates and facilitates the vasculature's embolization downstream [7,8]. Furthermore, the tumor may be protected by the attachment and

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stimulation of platelets by tumor cells and associated platelet-fibrin-rich network-cancer emboli. immunological system cells [4,9]. Moreover, platelets encourage the invasion of cancer cells into organs and tissues that are disease-free [10]. Tumor cells can produce several proteolytic enzymes that break down and reorganize the extracellular matrix (ECM) in order to penetrate [11].

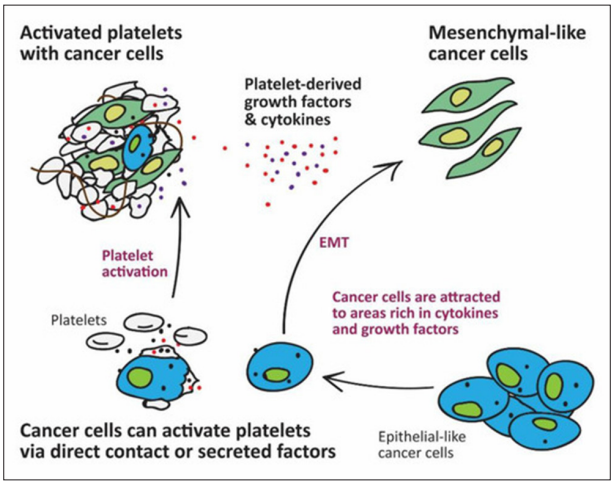

Figure 1: Platelets in Metastasis: Cancer cells can activate platelets. Activated platelets secrete growth factors and chemokines to attract other cancer cells to areas rich in survival factors. Platelet TGFβ1 induces EMT in cancer cells, which are characterised by an elongated shape and improved metastatic ability.

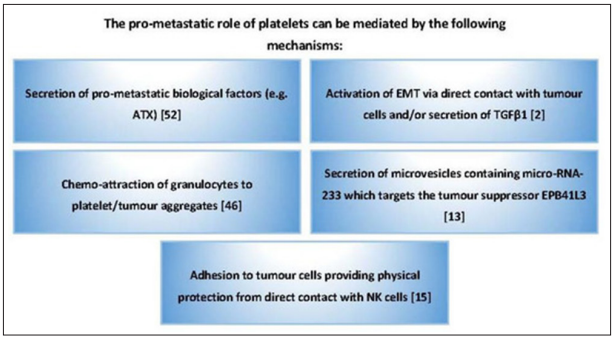

Figure 2: Summary of the pro-metastatic properties of platelets in cancer. Platelets promote cancer progression by releasing an array of pro-metastatic biological factors and by shielding cancer cells from NK-mediated cytotoxicity

Among these are zinc-dependent endopeptidases, or MMPs, which degrade extracellular matrix proteins. According to a recent study by our team, platelets promote the invasiveness of tumor cells by upregulating the production of MMP-9 [10]. The aim of this study was to investigate if platelets can enhance the survival of cancer cells that have been reduced by chemotherapeutic drugs such as Paclitaxel or 5-fluorouracil (5-FU). Both medications have been widely utilized for the therapy for ovarian and colorectal cancer that has spread. According to Sabharwal and Kerr, there have been recent critical assessments conducted on the necessity of administering a bolus injection to those individuals in order to attain extremely high plasma concentrations of the chemotherapy drugs [12]. In fact, it has been demonstrated that bolus injections of 5-FU raise its plasma levels in combination regimens surpassing 100 mg·mL-1 [13]. For the first time, our research demonstrates that, at clinically meaningful concentrations, platelets improve the survival of human ovarian and colonic adenocarcinoma cells treated with the anticancer medication's paclitaxel and 5-FU. Major pro-survival mechanisms implicated in this platelet impact have also been discovered.

Discussion

Our main discovery is that platelets boost the survival of adenocarcinoma cells when they are exposed to anticancer medications. This impact is more likely to happen in the bloodstream than in Caco-2 cells, especially in cells that have been treated with 5-FU. According to Martinek et al, ovarian cancer cells are well known for being resistant to chemotherapy [14]. This resistance may be attributed to a number of processes, including the activation of DNA-repairing pathways. Our study's concentrations match those that have been reported during the treatment of metastatic tumors. In fact, cancer has been treated more aggressively in recent years, requiring higher plasma concentrations than in the past. Bolus injections are used to treat metastatic cancer in an effort to It has recently been brought to light that mixed regimens are effective [13]. Furthermore, a review of preclinical studies indicates that high-dose, short-term 5-FU administration causes growth suppression of tumors resistant to traditional therapy [15]. It's also important to note that exposing human gingival fibroblasts to 5-FU resulted in cell death, albeit more gradually than in tumor cells. The fact that healthy cells do not divide as quickly as tumor cells may help to explain this. Furthermore, platelets demonstrated the ability to impede the impact of 5-FU on CRL2014 cells.

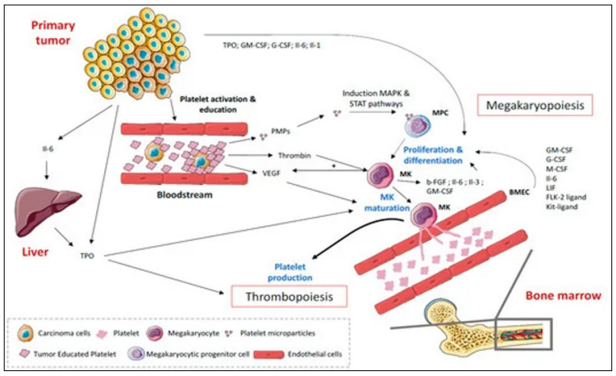

Figure 3: Mechanisms of cancer-associated thrombocytosis. This figure summarizes all the mechanisms involved in the production of platelets mediated by the primary tumor. BMEC: Bone Marrow Endothelial Cells. This figure was obtained using Servier medical art. http://smart.servier.com/. GM-CSF: Granulocyte-Macrophage Colony-Stimulating Factor; G-CSF: Granulocyte Colony-Stimulating Factor; M-CSF: Macrophage Colony-Stimulating Factor; Il-6: Interleukin-6; LIF: Leukemia Inhibitory Factor; FLK-2: Fetal Liver Kinase-2; Kit-ligand (Steel factor); TPO: thrombopoietin.

What Processes Might Platelets Initiate to Improve the Survival of Adenocarcinoma Cells Exposed to Anticancer Medications?

In the first place, platelets can adjust the equilibrium between genes that promote and inhibit apoptosis. Platelets shift the net balance in favor of apoptosis inhibition, according to an examination of the expression of genes that control apoptosis.

For instance, increased expression of NF-kB1 and NF-kB2 suggests that platelets activate NF-kB's anti-apoptotic pathway [16]. Second, platelets protect cancer cells from the cell cycle suppression caused by anticancer drugs. Furthermore, it has been established that platelet release from thrombin-activated platelets may have a significant impact on the cell cycle because it has been shown to enhance the migration and proliferation of osteogenic cultures of bone marrow cells [17]. In fact, when platelets are present during the cell cycle, the majority of 59 M ovarian cells are in the S and G2/M phases. Additionally, given the existence of Irreversible cell cycle arrest was avoided by platelet cells. We examined the levels of cyclin A, B1, D1, and E, the primary regulators of cell cycle progression whose overexpression has been found in a variety of cancers, in order to investigate the mechanisms underlying these effects of platelets on cell cycle [18-21].

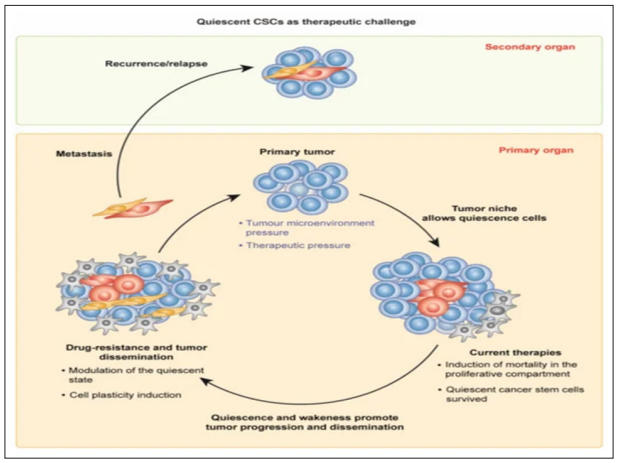

Figure 4: Quiescence in cancer stem cells. CSCs have the unique capacity to undergo a dormant state, making them invincible to external attack and preserving a reservoir of highly proliferative cells, which can recreate the entire tumor, if necessary

Furthermore, elevated levels of cyclins may be associated with cancer migration, invasiveness, metastasis, and unfavorable patient prognosis [22,23]. Endocrine resistance in breast cancer cells has also been connected to overexpression of cyclin D1 [18]. When platelets were present, we observed a marked up-regulation of cyclin A in the untreated and 59 M cells treated with 5-FU, throughout the whole cell cycle. In contrast, in cells treated with paclitaxel, platelets had no effect on the regulation of cyclin A. Paclitaxel's direct effect on cyclin A could account for this [24]. In 59 M cells treated with 5-FU but not paclitaxel, we observed a considerable up-regulation of cyclin B1, D1, and E levels in the presence of platelets, similar to cyclin A. Therefore, higher cyclin expression could be the reason behind platelets' ability to stimulate the cancer cell cycle. It's interesting to note that platelets significantly affected the cancer cell cycle in 59 M ovarian Caco-2 cells but not in colonic Caco-2 cells. This finding likely reflects the selectivity of the medication or the kind of cell.

Thirdly, DNA repair mechanisms are accelerated by platelets. Anticancer medications frequently cause harm of DNA, and this sets off chemical reactions that try to fix damage to DNA. Activated by phosphorylation, these include BRCA1, Chk1, Mre11, and p95/Nbs1, which coordinate DNA lesion repair with cell cycle stalling to facilitate DNA repair [25]. In fact, the BRCA1 protein is essential for detecting DNA damage and controlling cell cycle checkpoints, which permit cell cycle progression only following DNA repair and prevent hereditary damage transmission to cellular generations that follow [26]. The genomic integrity is preserved by the activation of checkpoint 1 (Chk1), which permits repair of DNA damage prior to its replication and transmission to daughter cells [27]. The proteins p95/Nbs1 and Mre11 identify the breaks in the DNA and trigger a range of other proteins involved in DNA repair and cell cycle regulation. Both homologous and non-homologous doublestrand break repair require the Mre11 and p95/Nbs1 complex [28,29].

We discovered that the presence of platelets raises the amounts of active DNA-repairing agents in both colonic and ovarian adenocarcinomas. Notably, this effect was notable in 5-FU but not in all of the repair mechanisms of cells challenged with paclitaxel, which is likely due to drug specificity once more Ultimately, JNK-p54 and p38 MAPKs are upregulated by platelets.

According to Dhillon et al, MAPKs, which include p38, p42/44, JNK-p46, and JNK-p54 MAPKs, mediate extracellular signals and regulate important cellular processes like proliferation, differentiation, survival, death, and migration [30]. We discovered that platelets are capable of to precisely activate these proteins in 59 M cells treated with paclitaxel and 5-FU.

What Substances Secreted into The Platelet-Cancer Secretome May Improve the Survival of Cancer Cells?

Through drug sequestration, platelets can restrict a chemotherapeutic agent's ability to reach cancer cells. In addition, platelets might offer an anti-apoptotic mechanism to offset anticancer medications' pro-apoptotic effects. Since Strieth et al could not detect any meaningful interactions between platelets and paclitaxel in vitro, the first possibility seems less likely [31]. It is possible to rule out drug sequestration as the only mechanism behind the observed protective effect since both intact and released platelets can shield cancer cells from chemotherapeutic agent-induced apoptosis. Nevertheless, entire platelets provided more protection than release. This could be explained by the fact that apoptosis can be modulated by factors related to platelet membranes. In fact, it has already been discovered that platelet surface membrane receptors are crucial in mediating the contacts between platelets and cancer cells [5,32].

Furthermore, elevated concentrations of platelet-derived microparticles enhance the survival of malignant hematopoietic cells and transfer a variety of surface receptors and adhesion molecules to target cells, which is associated with a bad prognosis for patients [33]. We employed proteomics to investigate platelet components that might shield cancer cells from harm the protein secretum generated when platelets interact with Caco-2 cells treated with Paclitaxel. It is known that certain proteins released by platelets can influence apoptosis.

These consist of TGF-b, RANTES, thrombospondin-1, and clusterin [34-36]. Clusterin is a glycoprotein that is overexpressed in certain types of cancer, such as colon, ovarian, and breast cancer. Research has shown that patients with clusterin have

a bad prognosis [37,38]. According to a study by Park et al., ovarian cancer cells with high clusterin expression levels are more resistant to paclitaxel [39,40]. However, clusterin had no discernible impact on Caco-2 cell survival in our experimental setup. Platelet a-granules contain thrombospondin-1 (TSP-1), which is released upon platelet activation [41]. TSP-1 has the potential to both promote and prevent cancer. This glycoprotein might limit tumor growth by acting as an antiangiogenetic factor neovascularization. TSP-1, on the other hand, is implicated in the invasion, migration, and adherence of cells within solid tumors. According to Qian and Tuszynski, human malignant tissues and cancer patients' plasma have elevated levels of TSP-1 expression. Poor patient prognosis is linked to higher levels of TSP-1 receptors on cancer cells [42]. TGF-b, which suppresses host immune responses by lowering IFN-g secretion and the cytotoxicity of natural killer cells, is also known to be activated by TSP-1 [43,45]. It's interesting to note that TSP-1 dramatically improved the Caco-2 cells' ability to survive when exposed to paclitaxel in our scenario. Additionally, we discovered that the chemokine RANTES, which stimulates the survival, invasion, and proliferation of cancer cells, had a comparable impact of TSP-1 [46]. But since cancer cells have also been shown to express RANTES, it is still unknown where this protein in the secretome originated in cancer cells or platelets [46]. It is important to note that the current experimental setting included platelets from healthy donors interacting with cancer cells. In the future, platelets from individuals with colon and ovarian malignancies will be used in research.

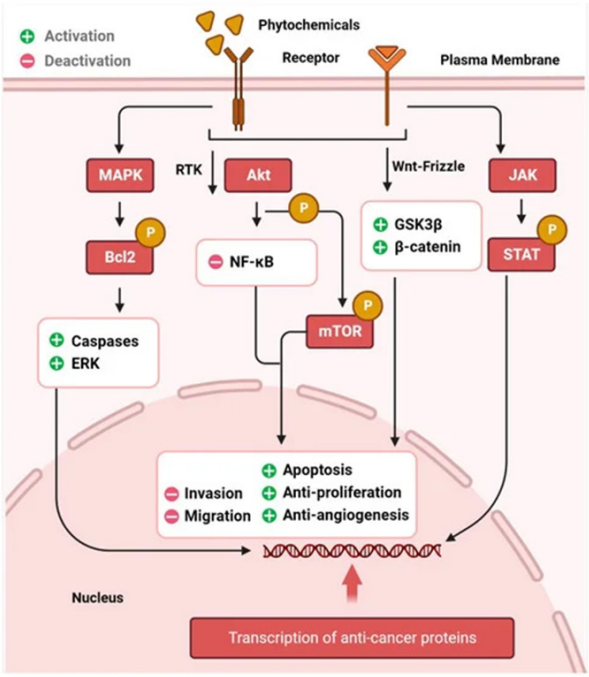

Figure 5: Cancer chemoprevention through the phytochemical interaction with signaling molecules. The image illustrates how phytochemicals activate MAPK, Akt, Wnt, and JAK/STAT pathways, leading to cancer cell death through many intracellular signaling molecules.

Our Research has Ramifications for Our Knowledge of The Mechanisms Behind Cancer's Resistance to Chemotherapy

Chemoresistance in cancer still poses a significant challenge to the use of anticancer medications [47]. The idea that interactions between malignant cells and the tumor microenvironment may affect cancer cells' apoptotic response and promote cell survival is supported by a number of lines of evidence. As an illustration, It has been demonstrated that when paclitaxel and 5-FU are used in conjunction with chemotherapeutics for colon cancer, prostate cancer, and breast cancer, inhibition of NF-kB, a major pro-inflammatory transcription factor, increases cancer cell susceptibility to these drugs [48-50]. Moreover, colonic carcinoma chemoresistance is reduced and paclitaxel-induced apoptosis is enhanced when the p42/44 MAPK is inhibited [51-57].

Conclusion

Our findings support the significance of interactions between cancer cells and platelets for the survival of adenocarcinomas treated with high concentrations of anticancer medications and offer a pharmacological justification for developing medications that modify platelets and cancer relationships.

Conflicts of Interest: None.

References

1. Akl EA, Barba M, Rohilla S, Terrenato I, Sperati F, et al. Anticoagulation for the long term treatment of venous thromboembolism in patients with cancer. Cochrane Database Syst Rev. 2008a. CD006650.
2. Pasquini E, Gianni L, Aitini E, Nicolini M, Fattori PP, et al. Acute disseminated intravascular coagulation syndrome in cancer patients. Oncology. 1995. 52: 505-508.
3. dos Santos VMD, Rodrigues DBR, Castro ECDC, Saldanha JC, Soares S, et al. Widespread hematogenous metastases and Trousseau's syndrome in gastric adenocarcinoma. Rev Hosp Clin Fac Med Sao Paulo, 2001. 56: 91-96.
4. Gupta GP, Massagué J. Platelets and metastasis revisited: a novel fatty link. J Clin Invest. 2004. 114: 1691-1693.
5. Jurasz P, Alonso-Escolano D, Radomski MW. Platelet-cancer interactions: mechanisms and pharmacology of tumour cell-induced platelet aggregation. Br J Pharmacol. 2004. 143: 819-826.
6. Radomski MW, Jenkins DC, Holmes L, Moncada S. Human colorectal adenocarcinoma cells: differential nitric oxide synthesis determines their ability to aggregate platelets. Cancer Res. 1991. 51: 6073-6078.
7. Mehta P. Potential role of platelets in the pathogenesis of tumor metastasis. Blood. 1984. 63: 55-63.
8. Bazou D, Santos-Martinez MJ, Medina C, Radomski MW. Elucidation of flow-mediated tumour cell-induced platelet aggregation using an ultrasound standing wave trap. Br J Pharmacol. 2011. 162: 1577-1589.
9. Gay LJ, Felding-Habermann B. Contribution of platelets to tumour metastasis. Nat Rev Cancer. 2011. 11: 123-134.
10. Alonso-Escolano D, Medina C, Cieslik K, Radomski A, Jurasz P, et al. Protein kinase Cd mediates platelet-induced breast cancer cell invasion. J Pharmacol Exp Ther. 2006. 318: 373-380.
11. Medina C, Radomski MW. Role of matrix metalloproteinases in intestinal inflammation. J Pharmacol Exp Ther. 2006. 318: 933-938.
12. Sabharwal A, Kerr D. Chemotherapy for colorectal cancer in the metastatic and adjuvant setting: past, present and future. Expert Rev Anticancer Ther. 2007. 7: 477-487.

13. Tamura T, Kuwahara A, Kadoyama K, Yamamori M, Nishiguchi K, et al. Effects of bolus injection of 5-fluorouracil on steady-state plasma concentrations of 5-fluorouracil in Japanese patients with advanced colorectal cancer. Int J Med Sci. 2011. 8: 406-412.
14. Martinek I, Haldar K, Gaitskell K, Bryant A, Nicum S, et al. DNA-repair pathway inhibitors for the treatment of ovarian cancer. Cochrane Database Syst Rev. 2010. CD007929.
15. Sobrero AF, Aschele C, Bertino JR. Fluorouracil in colorectal cancer - a tale of two drugs: implications for biochemical modulation. J Clin Oncol. 1997. 15: 368-381.
16. Annunziata CM, Davis RE, Demchenko Y, Bellamy W, Gabrea A, et al. Frequent engagement of the classical and alternative NF-[kappa]B pathways by diverse genetic abnormalities in multiple myeloma. Cancer Cell. 2007. 12: 115-130.
17. Kark LR, Karp JM, Davies JE. Platelet releasate increases the proliferation and migration of bone marrow-derived cells cultured under osteogenic conditions. Clin Oral Implants Res. 2006. 17: 321-327.
18. Kenny FS, Hui R, Musgrove EA, Gee JMW, Blamey RW, et al. Overexpression of cyclin D1 messenger RNA predicts for poor prognosis in estrogen receptor-positive breast cancer. Clin Cancer Res. 1999. 5: 2069-2076.
19. Hwang HC, Clurman BE. Cyclin E in normal and neoplastic cell cycles. Oncogene. 2005. 24: 2776-2786.
20. Rivera A, Mavila A, Bayless K, Davis G, Maxwell S. Cyclin A1 is a p53-induced gene that mediates apoptosis, G2/M arrest, and mitotic catastrophe in renal, ovarian, and lung carcinoma cells. Cell Mol Life Sci. 2006. 63: 1425-1439.
21. Zhao M, Kim YT, Yoon BS, Kim SW, Kang MH, et al. Expression profiling of cyclin B1 and D1 in cervical carcinoma. Exp Oncol. 2006. 28: 44-48.
22. Wegiel B, Bjartell A, Tuomela J, Dizeyi N, Tinzl M, et al. Multiple cellular mechanisms related to cyclin A1 in prostate cancer invasion and metastasis. J Natl Cancer Inst. 2008. 100: 1022-1036.
23. Aaltonen K, Amini RM, Heikkila P, Aittomaki K, Tamminen A, et al. High cyclin B1 expression is associated with poor survival in breast cancer. Br J Cancer. 2009. 100: 1055-1060.
24. Perez-Stable C. 2-Methoxyestradiol and paclitaxel have similar effects on the cell cycle and induction of apoptosis in prostate cancer cells. Cancer Lett. 2006. 231: 49-64.
25. Martin SA, Lord CJ, Ashworth A. DNA repair deficiency as a therapeutic target in cancer. Curr Opin Genet Dev. 2008. 18: 80-86.
26. Kennedy RD, Quinn JE, Mullan PB, Johnston PG, Harkin DP. The role of BRCA1 in the cellular response to chemotherapy. J Natl Cancer Inst. 2004. 96: 1659-1668.
27. Bolderson E, Richard DJ, Zhou B-BS, Khanna KK. Recent advances in cancer therapy targeting proteins involved in DNA double-strand break repair. Clin Cancer Res. 2009. 15: 6314-6320.
28. Lavin MF. The Mre11 complex and ATM: a two-way functional interaction in recognising and signaling DNA double strand breaks. DNA Repair. 2004. 3: 1515-1520.
29. Lavin MF. ATM and the Mre11 complex combine to recognize and signal DNA double-strand breaks. Oncogene. 2007. 26: 7749-7758.
30. Dhillon AS, Hagan S, Rath O, Kolch W. MAP kinase signalling pathways in cancer. Oncogene. 2007. 26: 3279-3290.
31. Strieth S, Nussbaum CF, Eichhorn ME, Fuhrmann M, Teifel M, et al. Tumor-selective vessel occlusions by platelets after vascular targeting chemotherapy using paclitaxel encapsulated in cationic liposomes. Int J Cancer. 2008. 122: 452-460.
32. Janowska-Wieczorek A, Wysoczynski M, Kijowski J, Marquez-Curtis L, Machalinski B, et al. Microvesicles derived from activated platelets induce metastasis and angiogenesis in lung cancer. Int J Cancer. 2005. 113: 752-760.
33. Helley D, Banu E, Bouziane A, Banu A, Scotte F, et al. Platelet microparticles: a potential predictive factor of survival in hormone-refractory prostate cancer patients treated with docetaxel-based chemotherapy. Eur Urol. 2009. 56: 479-485.
34. Schniewind B, Groth S, Sebens Muerkoster S, Sipos B, Schafer H, et al. Dissecting the role of TGF-beta type I receptor//ALK5 in pancreatic ductal adenocarcinoma: Smad activation is crucial for both the tumor suppressive and prometastatic function. Oncogene. 2007. 26: 4850-4862.
35. Bi J, Guo AL, Lai YR, Li B, Zhong JM, et al. Overexpression of clusterin correlates with tumor progression, metastasis in gastric cancer: a study on tissue microarrays. Neoplasma. 2010. 57: 191-197.
36. Borczuk AC, Papanikolaou N, Toonkel RL, Sole M, Gorenstein LA, et al. Lung adenocarcinoma invasion in TGF [beta] RII-deficient cells is mediated by CCL5/RANTES. Oncogene. 2007. 27: 557-564.
37. Wei L, Xue T, Wang J, Chen B, Lei Y, et al. Roles of clusterin in progression, chemoresistance and metastasis of human ovarian cancer. Int J Cancer. 2009. 125: 791-806.
38. Redondo M, Rodrigo I, Alcaide J, Tellez T, Roldan MJ, et al. Clusterin expression is associated with decreased disease-free survival of patients with colorectal carcinomas. Histopathology. 2010. 56: 932-936.
39. Park DC, Yeo SG, Wilson MR, Yerbury JJ, Kwong J, et al. Clusterin interacts with Paclitaxel and confer Paclitaxel resistance in ovarian cancer. Neoplasia. 2008. 10: 964-972.
40. Djeu JY, Wei S. Clusterin and chemoresistance. In: George FVW (ed.). Advances in Cancer Research. Academic Press: Tampa, Florida, USA. 2009. 77-92.
41. Packham MA, Mustard JF. Platelet adhesion. Prog Hemost Thromb. 1984. 7: 211-288.
42. Qian X, Tuszynski GP. Expression of thrombospondin-1 in cancer: a role in tumor progression. Proc Soc Exp Biol Med. 1996. 212: 199-207.
43. Tuszynski GP, Nicosia RF. The role of thrombospondin-1 in tumor progression and angiogenesis. Bioessays. 1996. 18: 71-76.
44. Murphy-Ullrich J, Poczatek M. Activation of latent TGF-beta by thrombospondin-1: mechanisms and physiology. Cytokine Growth Factor Rev. 2000. 11: 59-69.
45. Kopp H-G, Placke T, Salih HR. Platelet-derived transforming growth factor-b down-regulates NKG2D thereby inhibiting natural killer cell antitumor reactivity. Cancer Res. 2009. 69: 7775-7783.

46. Niwa Y, Akamatsu H, Niwa H, Sumi H, Ozaki Y, et al. Correlation of tissue and plasma RANTES levels with disease course in patients with breast or cervical cancer. Clin Cancer Res. 2001. 7: 285-289.
47. Pennington K, Pulaski H, Pennington M, Liu JR. Too much of a good thing: suicide prevention promotes chemoresistance in ovarian carcinoma. Curr Cancer Drug Targets. 2010. 10: 575-583.
48. Voboril R, Hochwald SN, Li J, Brank A, Weberova J, et al. Inhibition of NF-Kappa B augments sensitivity to 5-Fluorouracil/Folinic acid in colon cancer1. J Surg Res. 2004. 120: 178-188.
49. Kim S, Lee S, Yuk D, Moon D, Choi S, et al. Inhibition of NF-kB by ginsenoside Rg3 enhances the susceptibility of colon cancer cells to docetaxel. Arch Pharm Res. 2009. 32: 755-765.
50. Weldon CB, Burow ME, Rolfe KW, Clayton JL, Jaffe BM, et al. NF-[kappa]B-mediated chemoresistance in breast cancer cells. Surgery. 2001. 130: 143-150.
51. Xu R, Sato N, Yanai K, Akiyoshi T, Nagai S, et al. Enhancement of paclitaxel-induced apoptosis by inhibition of mitogen-activated protein kinase pathway in colon cancer cells. Anticancer Res. 2009. 29: 261-270.
52. Livak KJ, Schmittgen TD. Analysis of relative gene expression data using real-time quantitative PCR and the 2 [-delta delta CT] method. Methods. 2001. 25: 402-408.
53. Meyer N, Kim SS, Penn LZ. The Oscar-worthy role of Myc in apoptosis. Semin Cancer Biol. 2006. 16: 275-287.
54. Radomski A, Jurasz P, Sanders EJ, Overall CM, Bigg HF, et al. Identification, regulation and role of tissue inhibitor of metalloproteinases-4 (TIMP-4) in human platelets. Br J Pharmacol. 2002. 137: 1330-1338.
55. Radomski M, Moncada S. An improved method for washing of human platelets with prostacyclin. Thromb Res. 1983. 30: 383-389.
56. Thompson A, Shafer J, Kuhn K, Kienle S, Schwarz J, et al. Tandem mass tags: a novel quantification strategy for comparative analysis of complex protein mixtures by MS/MS. Anal Chem. 2003. 75: 1895-1904.
57. Treumann A, Thiede B. Isobaric protein and peptide quantification - perspectives and issues. Expert Rev Proteomics. 2010. 7: 647-653.