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Study on mechanism of cell cycle arrest induced by alkaloids in tumor cells

Ji Yubin[1,2*], Zhang Yao[1], Yu Miao[1,2], Li Wenlan[1,2]

[1]Center of Life Science and Environmental Science, Harbin University of Commerce, (HARBIN CHINA)

[2]Engineering Research Center of Natural Anti-tumor Drugs, Ministry of Education, (HARBIN CHINA)

138 Tongda Street, Daoli District, Harbin, Heilongjiang, Postcard: 150076, (CHINA)

E-mail: yumiao913@163.com

ABSTRACT

Alkaloids have strong anti-tumor activity. Recent studies have found that when subjected to the tumor cell cycle arrest, inhibit cell proliferation. Through literature review and abroad, will affect the alkaloids on different tumor cell cycle summarized to reveal alkaloids by blocking tumor cell anti-tumor mechanism of action, provide a theoretical basis for the future development of anti-tumor drugs and research ideas.

KEYWORDS

Alkaloids; Anti-tumor; Tumor cell; Cell cycle; Mechanism.

INTRODUCTION

Alkaloids are a class of nitrogen-containing organic compounds present in plants and animals, but mainly concentrated in nature plants. Alkaloids have a certain effect on central nervous system, cardiovascular system, immune system and also has anti-inflammatory anti-bacterial, anti-viral, Protect the liver, insecticidal and anti-tumor effects, etc. The study found a variety of alkaloids have some anti-tumor activity, such as camptothecin, paclitaxel and other anticancer drugs have clinical application and achieved certain results. The study found that alkaloids can exert antitumor effects by blocking the cell cycle. Cell cycle checkpoints can be divided into three categories, namely G_1, S and G_2 phases of the checkpoint In the process of cell replication checkpoint plays a different role in different. G_1 phase checkpoint primarily to delay or block cell transition to S phase, S phase checkpoint mainly in the S phase of DNA replication so that the child's starting rate slowed, while the G_2 checkpoint major slowdown in this phase cells enter mitosis. In the process of cell replication, the cell cycle-related proteins affect cell proliferation. P21 is a tumor suppressor gene important in cells, may play a role in multiple aspects of cell cycle. Based on the findings, P21 expression in tumor cells is typically lower than the normal cells. In addition, cell cycle regulation, cell cycle-dependent protein kinases (CDKs) and cyclins also plays an important role. Cyclins can specifically activate the CDKs, CDKs specific activation in different periods of the cell cycle can be successfully completed. Conclusion, the cell cycle-related indicators affect cell growth and proliferation through the regulation of the cell cycle arrest of tumor cell proliferation and thus is important targets of cancer treatment. This article focused on the effects of different tumor cell cycle alkaloids summarize, hoping the anti-tumor mechanism of action, and to provide some basis for revealing the alkaloids antitumor drug development.

HEPG-2

Yue Fan et al[1] found that matrine on hepatoma HepG-2 cells inhibited the proliferation, With increasing time of administration and concentration, HepG-2 cells in G_1 phase cells increased, The S-phase cells decreased, Description MATRINE will HepG-2 cells were arrested in G_1 phase. Secretary Vico et al[2] to further explore the role of matrine HepG-2 cells on the mechanism, Cell cycle by immunohistochemistry primarily in the regulation of the expression of G_1 phase correlation factor expression. The results showed that matrine by upregulating negative regulator of cell cycle P53, Rb, P21, P27, P16, down regulate the expression of positive factors CyclinD1 will HepG-2 cells were arrested in G_1 phase to exert anti-tumor effects. Jin Yan shu[3] found that matrine could significantly inhibit human hepatoma Bel-7402 cells and induce apoptosis. Flow cytometry results showed that matrine can Bel-7402 cells were arrested in G_0-G_1 phase.

Present in the eukaryotic cells of the micro tube, which on the maintenance of cell shape, cell division and cell signal transduction plays an important role. GAO Shi-Yong et al[4] observed cell tubulin found that when Evodiamine hepatoma HepG-2 cells, intracellular tubulin polymerization state changes, cells were distributed bundles interference spindle formation cell cycle arrest in G_2/M phase. In addition, Kuo et al.[5] To observe the effect of tetrandrine on HepG-2 hepatoma cell cycle showed upregulation of tetrandrine HepG-2 cells P53 and P21/WAF1 expression and cell cycle arrest in G_1 phase. Strychnine also be HepG-2 cells were arrested in G_0/G_1[6] period.

GASTRIC

Zong yongli et al[7] found that gastric by celandine red base with BGC-823 cells, and its effect was significantly inhibited proliferation. The results showed that BGC-823 cells in S and G2/M arrest, which may celandine red base inhibition of mitochondrial respiration, energy transfer and inhibition of tubulin polymerization, the cell mitosis is not normally related. Some of cyclin closely associated with G2/M phase, such as CDK1 and Cyclin B1 and so on. It was found that the threonine residue 14 on the CDK1 phosphorylation can inhibit CDK1 high CDK1 activity. Inhibition of CDK1 activity, as well as CDK1 and Cyclin B1 complexes inhibit activation can make cells G2/M phase arrest. JI Yu-bin et al[8] found that chelidonine can stomach cancer SGC-7901 cells were arrested in G2/M phase, and its mechanism mainly downregulated SGC-7901 cells CDK1 and Cyclin B1 protein, increased p-CDK1 (Thr14) protein.

Law enforcement Dove et al[9] found that BGC-823 gastric cancer cell cycle has a certain timeliness, when the role of HCPT BGC-823 cells 24 hours, there G1 arrest. 48 hours later, the emergence of S and G2/M phase arrest. This role aging characteristics and semi-synthetic product camptothecin, irinotecan role in colon cancer cells have similarities[10]. Lou Jinli found that berberine on human gastric carcinoma BGC-823 cell cycle have significant organizational role, and with the increase in dose, the inhibition rate was significantly increased,and effectively arrest in G0/G1 phase.

OVARIAN CANCER

It was found that berberine can make a variety of tumor cells in cell cycle arrest occurs, the process is more complicated. Berberine generally tumor cells arrest in G1 phase or G2/M phase. xu gung wei found that ovarian cancer HEY, SKOV3 cells after treatment by berberine, G1 phase cells increased significantly. Further explore the mechanism found berberine can upregulate the expression of P21 and down Cyclin E. Explained by the action of berberine HEY, SKOV3 cells in G1 phase associated protein to inhibit tumor cell proliferation[11].

Anticancer mechanism of action of paclitaxel primarily by binding to specific sites on tubulin, promote and stabilize tubulin, make certain the role of microtubules affected, can not carry out normal mitosis and play a role. Currently, the clinical application of paclitaxel in the treatment of ovarian cancer has been the effect is significant. Incidence of malignant tumors are often associated with cell cycle regulation disorders. Research shows that when the down-regulation of the expression of Cyclin D1, not only can the cell cycle changes, but also reduces the cell resistance, enhance the effects of chemotherapy drugs. Han shiyu et al[12] found that paclitaxel down Cyclin D1 protein expression in ovarian cancer 3AO, so that tumor cells arrest and played anti-tumor effect. When combined with paclitaxel and LY294002, the better. In addition, Han xiaobing et al[13] Effects of of tetrandrine on the A2780 human ovarian cancer cell apoptosis and found that of tetrandrine can A2780 cells cell cycle arrest, arrest in G0/G1 phase, and its mechanism and tetrandra base raised P53,P21,the cell cycle-dependent kinase inhibition related.

MCF-7

Tumor cell growth is dependent on the normal operation of the cell cycle, and abnormal changes in microtubule-associated proteins and inhibit tumor cell proliferation. Studies confirm, α- tubulin and MAP-2 can maintain the normal structure of microtubules and stabilize microtubules, abnormal expression of both inducible cell mitotic arrest. JI Yu-bin et al[14] by studying the effects of solanine breast cancer MCF-7 cells were found in the microtubule system, solanine MCF-7 cells up-regulated microtubule α- tubulin and MAP-2 protein expression, the cells resistance stagnation in the S phase.

Thoennissen et al[15] reported that capsaicin inhibited the proliferation of breast cancer has, can make breast cancer cell cycle arrest at G0/G1 phase. The mechanism may be related to capsaicin reduce HER-2 protein expression and human epidermal growth factor receptor, reduced extracellular signal-regulated kinase and inhibition of cyclin D1 activation. Pei xiao-gaung et al[16] found that of tetrandrine can block human breast cancer MCF-7 cell cycle activity, so G2/M phase cells increased, S phase cells decreased, thus inhibiting DNA synthesis in MCF-7 cells. When of tetrandrine conjunction with arsenic trioxide, better than of tetrandrine alone[17].

LEUKEMIA

Lycorine can inhibit a variety of leukemia cell proliferation. Typically, the transcriptional activation of P21 rely mainly on P53, but it is not the only way. It was found that, in the absence of P53 in HL-60 leukemia cells, P21 can be activated by other means. P21 can control Cdk2/CyclinE complex and Cdc2 (Cdk1)/Cyclin B complex activity, so that cell cycle arrest to prevent the occurrence of mitosis. Shi Bi Wei[18] found that within Lycorine by upregulating protein P21 HL-60 cells, down Cdk2, Cdc2, Cyclin E protein to prevent HL-60 cell cycle.

plk1 mitotic kinases are important DNA damage checkpoint, on cell cycle arrest repair, maintain normal cell mitosis plays an important role. γ- tubulin protein is a key mitotic centrosome formation. Michael and other leukemia K562 cells with vincristine and these two proteins were tested and found vincristine plk1 aggregation by inhibiting tubulin and γ- the K562 cells were arrested in G2/M phase. Zhu da-chenget al[19] found that when vincristine leukemia CEM cells, G2/M phase cells decreased, S phase cells relative increase, indicating that it may inhibit CEM cell mitosis and anti-tumor effect.

In addition, Zhang Yongqing et al[20] studied the mechanism of matrine on K562 cells found in K562 matrine down 16 genes, of which 11 are Cyclins or CDKs cycle-related genes and molecules, up 19 genes, there are 16 pro-apoptotic genes or gene families CKIs.

CONCLUSIONS

Alkaloids are present in the natural flora and fauna and mushrooms in the amine molecules. Many alkaloids are human or animal pharmacological response, especially for tumor cells, in recent years has also been widely used in clinical practice. Alkaloids by regulating cell cycle arrest tumor cell proliferation and thus also an important role in the treatment of cancer targets. Alkaloids common structure types are pyridine, tropane, isoquinoline, indole, terpenoids, steroids, and organic amines.

Pyridine alkaloids, mainly west pyridine class structure type chloroquine Well, the chloroquine Well in West pyridine human hepatoma cell type can be blocked in G1 phase in human leukemia cell line K562 can be arrested in S phase. As matrine, matrine negatively regulated by cell cycle regulators P53, Rb, P21, P27, P16, down regulate the expression of positive factors CyclinD1 will HepG-2 cell cycle arrest in G1 phase to exert anti-tumor effects. Bel-7402 can also be cell cycle arrest in G0-G1 phase. And for leukemic K562 cells, the matrine Cyclins or CDKs down in molecular genetics K562, thus proving effectively blocked in S phase.

Isoquinoline alkaloids, into benzyl isoquinoline, double-benzyl isoquinoline, original berberine, morphine and benzophenanthridine class. Where the double-benzyl isoquinoline type alkaloids can be breast cancer cells arrested in S phase or G2/M phase, HepG-2 cells can be blocked in G1 phase cell cycle arrest in ovarian G0/G1 phase. As Tetrandrine factors, in combination with cisplatin by the surface structure of cell membranes of cancer cells are destroyed, voids, surface particle size increases, S phase arrest obvious. Tetrandrine. By upregulating HepG-2 cells in the P53 and P21/WAF1 expression, the cells can be blocked in G1 phase. Tetrandrine by upregulating P53,P21,cell cycle-dependent kinase inhibition, can A2780 cells cell cycle arrest, and arrest in G0/G1 phase of breast cancer MCF-7 cells may also occur blockade and arrest in G2/M

phase. Original type alkaloid berberine human gastric cancer cells can be effectively blocked in 7901 G0/G1 phase, the ovarian cell cycle arrest in G1, G2/M phase, such as ovarian cancer berberine may be effectively blocked in G2/M phase. Of gastric cancer cells increased with the dose detected arrest in G0-G1 phase. Opiates can MCF-7 cells were arrested in G0/G1 phase, such as morphine can induce MCF-7 cells were mainly arrested at G0/G1 phase, and the concentration of morphine administered in a dose relationship. Benzophenanthridine alkaloids can be BGC-823, 7901 gastric cancer cells were arrested in S, G2/M phase, such as chelerythrine base, by inhibiting tubulin polymerization inhibition of CDK1 and Cyclin B1 activity, gastric 7901 mitosis can not be normal.

Indole alkaloids can be divided into tryptamine indoles, monoterpene indole and dimeric indole. Tryptamine indoles which can induce human hepatoma cell HepG-2 cells were arrested in G2/M phase arrest in colon cancer cells in S phase. As Evodiamine, spindle formation by interfering with the liver arrest in G2/M phase. Colon cancer cells by down-regulating the LOVO CyclinA, CDK2 expression, protein expression and reduced cdc25c inhibit Cyclin B/CDK1 expression of cell cycle arrest in S phase. Single stick indole alkaloid structure can effectively HepG-2 cells were arrested in G0/G1 phase, as Strychnos alkaloids contained by inhibiting cyclin family of proteins which proves the arrest period. Dimeric indole alkaloids can be K562 cells were arrested in G2/M phase. Such as vincristine CEM cells by inhibiting mitosis, thus K562 cells were arrested in G2/M phase, effective drug for the treatment of leukemia.

Terpene alkaloids, such as paclitaxel, may be ovarian cancer, breast cancer arrest in G2/M phase, and with prolonged drug action and blockade enhanced.

Steroidal alkaloids can MCF-7 human breast cancer cells in the S phase arrest, such as solanine inhibit S phase typical tubulin -á, thus proving its cycle blockade.

Organic amine alkaloids vanilla amides can be MCF-7 cells and human bladder cancer cells were effectively blocked in G0/G1 phase, such as capsaicin can be raised through G0/G1 phase of the cyclin-dependent kinase inhibitor, effectively rendering apoptosis.

Relationship between cell cycle and cancer concern, malignant disorders related to proliferation and cell cycle, regulation of cell cycle control point with different cell cycle-related period, mainly G1/S phase, G0-G1 phase, G2/M period. In this paper, different alkaloids from different tumor cells were analyzed, the study found chloroquine Well in West pyridine class structure type alkaloids, such as matrine can inhibit telomerase in tumor cells, which is a ribonucleoprotein complex after activation can promote unlimited cell proliferation, especially liver cancer cells, matrine HepG-2 cells inhibited telomerase activity, inhibition of cell proliferation, it is widely used matrine in hepatoma cells. The former type of alkaloid berberine on human cancer, leukemia, liver cancer, stomach cancer in vitro experiments have proved that it has cycle arrest. Clinically for the treatment of gastrointestinal diseases, primarily pharmacological activity berberine is berberine, its U937, B16 cells have significant anti-tumor activity effect. The dimeric indole alkaloids to inhibit the proliferation of leukemia, the treatment of leukemia and efficient drug, is widely used in clinical practice. But the study of alkaloid drugs on tumor cells is not very in-depth, so it should be more in-depth, systematic and comprehensive study to better clinical application, provide the theoretical basis for the development of natural medicin.

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