



Establishment of optimal regulatory network of colorectal cancer based on p42.3 protein

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ABSTRACT

Objective: to establish regulatory network of colorectal cancer involving p42.3 protein and to provide theoretical evidence for deep functional exploration of p42.3 protein in the onset and development of colorectal cancer. **Methods:** with protein similarity algorithm, reference protein set of p42.3 cell apoptosis was built according to structural features of p42.3. GO and KEGG databases were used to establish regulatory network of tumor cell apoptosis involving p42.3; meanwhile, the largest possible working pathway that involves p42.3 protein was screened out based on Bayesian network theory. Besides, GO and KEGG were used to build regulatory network on early diagnosis gene markers for colorectal cancer including WWOX, K-ras, COX-2, p53, APC, DCC and PTEN, at the same time, a regulatory network of colorectal cancer cell apoptosis which involves p42.3 was established. **Results:** cell apoptotic regulatory network that p42.3 participates in primarily consists of Bcl-2 family genes and the largest possible pathway is p42.3 → FKBP → Bcl-2 centered as FKBP protein. Combined with colorectal cancer regulatory network that involves early diagnosis gene markers, it can be predicted that p42.3 is most likely to regulate the colorectal cancer cell apoptosis through FKBP → Bcl-2 → Bax → caspase-9 → caspase-3 pathway. **Conclusion:** the colorectal cancer apoptosis network based on p42.3 established in the study provides theoretical evidence for deep exploration of p42.3 regulatory mechanism and molecular targeting treatment of colorectal cancer.

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1. Introduction

Colorectal cancer is a worldwide high-incidence tumor. GLOBOCAN 2012 data show that (International Agency for Research on Cancer, 2012) the global number of colorectal cancer cases ranks the third in malignant tumors, second to lung cancer, breast cancer; its death ranks the fourth in malignant tumors, second to lung cancer, liver cancer and gastric cancer. Chen Wanqing et al. showed in a domestic survey that (Chen et al., 2016), colorectal cancer has become China's third largest malignant tumor, showing multiple tumors in men and women, and incidence and mortality of the dis-

ease were on the rise during 2000 and 2011. Age of onset of colorectal cancer in China is mostly 40–60 years. Due to insidious onset of colorectal cancer, early symptoms are not valued, and then the majority of patients are in late stage when it is diagnosed, with metastasis in about 25% patients. Therefore, in-depth exploration of onset and development mechanism of colorectal cancer means great significance for prevention and treatment of the disease. p42.3 gene was first discovered and cloned by Xu et al. (2007). The gene was found to be highly expressed in tumor and embryonic tissue, but not expressed in adult tissue. Subsequent studies showed that p42.3 was highly expressed in colorectal cancer tissue as independent prognostic factor of colorectal cancer (Yuan et al., 2013). The structure of p42.3 protein was analyzed and found in earlier stage to have two typical structural domains of EF-hand and CC-Domain. With protein structure similarity algorithm, reference protein set of p42.3 was built, and the regulatory network (Zhang et al., 2012; Zhang et al., 2013; Hao et al., 2015) for p42.3 involvement in tumor cell proliferation was constructed on this basis, but its regulatory pathways in colorectal cancer remains unclear.

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In the previous study, the seven genetic markers for early diagnosis of colorectal cancer were screened out by Meta analysis, including WWOX, K-ras, COX-2, p53, APC, DCC and PTEN, which were then studied in different directions. Zhang Jihua's team predicted the action target of traditional Chinese medicine (Tian et al., 2017). Hao Yibin's team conducted in-depth exploration of colorectal cancer regulation mechanism (Hao et al., 2017). The research group plans to build a more complete colorectal cancer regulatory network on this basis by combining p42.3.

2. Materials and methods

2.1. Establishment of regulatory network for p42.3 involvement in tumor cell apoptosis

2.1.1. Establishment of reference protein set p42.3

The apoptosis-related reference protein set for p42.3 was established using the protein similarity algorithm model (Zhang et al., 2012). First, a certain amount of protein pdb structure files were collected in the RCSB PDB (<http://www.rcsb.org/pdb/home/home.do>) database, and then similarity of each pair of proteins was calculated by MATLAB regarding 9 aspects of space density, total number of atoms, number of amino acids, number of amino acids species, the ratio of C, N, O, and interior spatial position of P and S in protein molecule. The sequence homology of each pair of proteins was obtained by BLAST, then nonlinear algorithm model involving sequence homology and similarity of parameters was established with neural network, the model could be trained by the collected data. Finally, the similarity between p42.3 protein and reference protein was calculated by using the model, and p42.3 apoptosis related reference protein set was established by using apoptosis-related function as screening condition.

2.1.2. Construction of p42.3 apoptotic regulatory network

Using the reference protein as the starting point and cell apoptosis as the end point, the primary regulatory network of p42.3 protein-related cell apoptosis was established by using bioinformatics methods such as GO (Gene Ontology), KEGG (Kyoto Encyclopedia of Genes and Genomes) and literature search & disposal. With the similarity of reference protein and p42.3 protein as prior probability of the initial node, the probability of p42.3 participation in each path was calculated by Bayes' theorem and Bayesian regulatory network model was established. The maximum probability pathway in the regulatory network was used as the largest possible regulatory pathway of p42.3 protein in the process of cell apoptosis. The specific method is to take similarity of reference protein and p42.3 protein as prior probability of the initial node, and then calculate probability of occurrence of each node event through conditional probability, until the occurrence of end point - apoptosis.

2.2. GO analysis

Go to AmiGO's home page (<http://geneontology.org/>). With the screening condition Taxon as "Homo sapiens", preliminary analysis of GO function annotation was respectively performed for p42.3 reference protein and the seven genetic markers obtained by Meta analysis, including WWOX, K-ras, COX-2, p53, APC, DCC, PTEN.

2.3. KEGG analysis

Go to the home page of the KEGG signal pathway database (<http://www.kegg.jp/kegg/pathway.html>). With screening condition organism as "hsa", signal pathways associated with apoptosis

were searched by keywords of p42.3 reference protein, WWOX, K-ras, COX-2, P53, APC, DCC and PTEN.

3. Results

3.1. Establishment of p42.3 reference protein set

The proteins functionally related to cell apoptosis and with the same domain as p42.3 protein were screened. These proteins were used as reference proteins of p42.3 protein in tumor onset and development, and their similarity with p42.3 protein was calculated, with results shown in Table 1.

3.2. Establishment of regulatory network for p42.3 involvement in tumor cell apoptosis

Using the reference protein as the starting point and the function realization of cell apoptosis as the end point, the regulatory network of tumor cell apoptosis involving p42.3 (Fig. 1) was established. Where, "FKBP → Bcl-2 → cell apoptosis" is the highest possible acting path, and p42.3 is most likely to participate in the process of tumor cell apoptosis through FKBP and Bcl-2.

3.3. GO analysis results of genetic markers

Gene ontology (GO) is mainly divided into biological process (biological_process), molecular function (molecular_function) and cellular component (cellular_component) based on the role of genes and proteins in cells. Table 2 shows the GO analysis of WWOX and COX-2. WWOX is involved in p53-mediated apoptotic signaling pathway, Wnt signaling pathway, etc.; COX-2 only plays an important role in biological processes and molecular functions, and participates in biological processes of cyclooxygenase pathway, inflammatory response and blood pressure regulation, etc. Table 3 shows the annotation results of p53 and APC. P53 plays an important role in biological processes and cellular components, participates in the process of apoptosis and plays a positive regulatory role in the apoptotic signal pathway. APC participates in the apoptosis process and promotes apoptosis. Table 4 shows GO results of DCC and PTEN. DCC plays an important role in biological processes and cellular components, and positively regulates apoptotic signal pathway. PTEN has three functions: biological process, molecular function and cellular component. It plays a role in biological processes such as T cell receptor signal pathway, phosphoinositol metabolism process and phospholipid metabolism. However, function annotation of the human K-ras gene has not been found.

Table 1
p42.3 reference protein in the regulatory pathways of cell apoptosis.

| Code | Similarity | Same structure domain | Functional classification |
|---------|------------|-----------------------|---------------------------------|
| S100A11 | 0.8102 | EF | Cell proliferation, apoptosis |
| RAS | 0.8068 | EF | Cell proliferation, apoptosis |
| S100A2 | 0.7046 | EF | Cell proliferation, apoptosis |
| CIB1 | 0.7026 | EF | Cell proliferation, apoptosis |
| PAK1 | 0.6716 | CC | Cell apoptosis |
| S100B | 0.3095 | EF | Cell apoptosis |
| S100A4 | 0.2599 | EF | Cell differentiation, apoptosis |

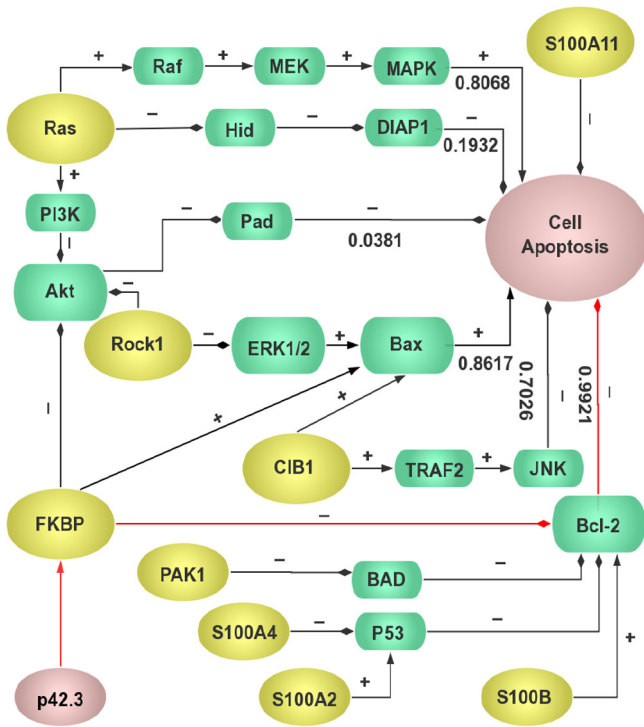


Fig. 1. Regulatory network for p42.3 involvement in tumor cell apoptosis (red pathway indicates the maximally possible acting pathway).

Table 2
GO analysis results of WWOX and COX-2.

| Gene | Gene ontology | GO Number | Name | |
|--------------------|------------------------------|--------------------|---|--|
| WWOX | biological_process | GO:0072332 | Intrinsic apoptotic signaling pathway by p53 class mediator | |
| | | GO:0016055 | Wnt signaling pathway | |
| | | GO:0001649 | Osteoblast differentiation | |
| | | GO:2001241 | Positive regulation of extrinsic apoptotic signaling pathway in absence of ligand | |
| | | GO:0097191 | Extrinsic apoptotic signaling pathway | |
| | | GO:0048705 | Skeletal system morphogenesis | |
| | | cellular_component | GO:0005829 | Cytosol |
| | | GO:0005794 | Golgi apparatus | |
| | | molecular_function | GO:0005515 | Protein binding |
| | | COX-2 | biological_process | GO:0019371 |
| GO:0006954 | Inflammatory response | | | |
| GO:0008217 | Regulation of blood pressure | | | |
| GO:0006979 | Response to oxidative stress | | | |
| GO:0055114 | Oxidation-reduction process | | | |
| Molecular_function | GO:0004601 | | | Peroxidase activity |
| | GO:0004666 | | | Prostaglandin-endoperoxide synthase activity |
| | | GO:0020037 | Heme binding | |

3.4. Establishment of regulatory network for p42.3 involvement in colorectal cancer cell apoptosis

KEGG analysis of WWOX, K-ras, COX-2, p53, APC, DCC, PTEN DNA markers by KEGG signal pathway database showed that p53, APC, DCC and K-ras were involved in the colorectal cancer regulatory network model. Combined with GO and KEGG analysis results of PTEN, COX-2, WWOX, the three were added to the col-

Table 3
GO analysis results of p53 and APC.

| Gene | Gene ontology | GO number | Name | |
|--------------------|---|----------------------|--|-------------|
| p53 | biological_process | GO:1900740 | Positive regulation of protein insertion into mitochondrial membrane involved in apoptotic signaling pathway | |
| | | GO:0007219 | Notch signaling pathway | |
| | | GO:0007596 | Blood coagulation | |
| | | GO:0006915 | Apoptotic process | |
| | | GO:0000075 | Cell cycle checkpoint | |
| | | GO:0033554 | Cellular response to stress | |
| | | GO:0097193 | Intrinsic apoptotic signaling pathway | |
| | | GO:0006977 | DNA damage response, signal transduction by p53 class mediator resulting in cell cycle arrest | |
| | | cellular_component | GO:0005654 | Nucleoplasm |
| | | APC | biological_process | GO:0043065 |
| GO:0008285 | Negative regulation of cell proliferation | | | |
| GO:0016477 | Cell migration | | | |
| GO:0000281 | Mitotic cytokinesis | | | |
| GO:0007026 | Negative regulation of microtubule depolymerization | | | |
| GO:0030178 | Negative regulation of Wnt signaling pathway | | | |
| GO:0007050 | Cell cycle arrest | | | |
| GO:0006974 | Cellular response to DNA damage stimulus | | | |
| cellular_component | GO:0005737 | | | Cytoplasm |
| GO:0005634 | Nucleus | | | |
| molecular_function | GO:0008013 | Beta-catenin binding | | |

orectal cancer regulatory network to construct the primary apoptosis regulatory network model of colorectal cancer as shown in Fig. 2. Meanwhile, by combining regulatory network for P42.3 involvement in apoptosis of tumor cells, the regulatory network model for p42.3 involvement in colorectal cancer cell apoptosis was constructed and optimized. As shown in Fig. 3, p42.3 is most likely to regulate colorectal cancer cell apoptosis via “FKBP → Bcl-2 → Bax → caspase-9 → caspase-3”.

4. Discussions

Colorectal cancer is a genetic disease that reflects multi-stage long-term evolution process of proto-oncogene activation and tumor suppressor gene inactivation under the action of environmental factors. Due to insidious onset of colorectal cancer, the symptoms gain low public awareness and many patients are already in the late stage when it is diagnosed. The disease will eventually progress to metastatic colorectal cancer in up to 50% newly diagnosed patients and less than 5% of patients who have metastasized can survive for over 5 years. The treatment effect is poor for patients with middle and advanced colorectal cancer. Its poor prognosis seriously affects patients' quality of life, bringing huge economic burden to cancer patients and their families (Al-Shuneigat et al., 2011). Therefore, it means great significance to explore the onset, development of colorectal cancer from genetic level. p42.3 is a colorectal cancer-associated gene. After p42.3 expression is interfered, there are obvious morphological changes of tumor cells. Specifically, growth is inhibited, clonal ability and tumorigenicity are affected, and M phase key gene CycinB1 and Chk2 of cell cycle can be regulated, which is closely related to mitosis and cell cycle (Xu et al., 2007). At the same time, p42.3 can affect APC protein active site, and then involve relevant cell signal pathway and biological function (Cao et al., 2015).

Table 4
GO analysis results of DCC and PTEN.

| Gene | Gene ontology | GO number | Name | |
|------|--------------------|--------------------|--|--|
| DCC | biological_process | GO:0043065 | Positive regulation of apoptotic process | |
| | | GO:0007411 | Axon guidance | |
| | cellular_component | GO:0097190 | Apoptotic signaling pathway | |
| | | GO:0005829 | Cytosol | |
| | | GO:0005886 | Plasma membrane | |
| PTEN | biological_process | GO:0050852 | T cell receptor signaling pathway | |
| | | GO:0048011 | Neurotrophin TRKreceptor signaling pathway | |
| | | GO:0043647 | Inositol phosphatemetabolic process | |
| | | GO:0007173 | Epidermal growth factor receptor signaling pathway | |
| | | GO:0008543 | Fibroblast growth factor receptor signaling pathway | |
| | | GO:0006661 | Phosphatidylinositol biosynthetic process | |
| | | GO:0048015 | Phosphatidylinositol-mediated signaling | |
| | | GO:0044281 | Small molecule metabolic process | |
| | | GO:0006644 | phospholipid metabolic process | |
| | | GO:0038095 | Fc-epsilon receptor signaling pathway | |
| | cellular_component | GO:0045087 | Innate immune response | |
| | | GO:0005829 | Cytosol | |
| | | molecular_function | GO:0016314 | Phosphatidylinositol-3,4,5-trisphosphate3-phosphatase activity |
| | | | GO:0051717 | Inositol-1,3,4,5-tetrakisphosphate 3-phosphatase activity |
| | | GO:0051800 | Phosphatidylinositol-3,4-bisphosphate 3-phosphatase activity | |

In this study, bioinformatics analysis was used to screen out proteins associated with tumor cell apoptosis and having the same

EF-hand or CC-domain structure domain as p42.3 protein. With these proteins as reference proteins, the similarity between reference protein and p42.3 was evaluated by using multi-parameter similarity calculation mode based on neural network. The primary regulatory network of cell apoptosis involving p42.3 protein-related reference protein was established by bioinformatics technique such as GO and KEGG. The maximum possible pathway of p42.3 protein in the primary regulatory network during apoptosis was screened by Bayes' theorem. As shown in Fig. 1 (red line), the “p42.3 → FKBP → Bcl-2” pathway with FKBP protein as the intermediate node is the largest possible pathway of p42.3 protein involvement in apoptosis. Bcl-2 protein family can be divided into anti-apoptotic subfamily and pro-apoptotic subfamily, and Bcl-2 and Bax are the main anti-apoptotic and pro-apoptotic proteins respectively. A large number of previous studies have found that increased Bcl-2 protein expression results in increased protein ratio of Bcl-2 and Bax, in which case the cell apoptosis can be inhibited; on the contrary, if the Bax protein expression increases, Bcl-2 and Bax protein ratio will decline, which is likely to promote the occurrence of apoptosis (Galluzzi et al., 2016). In order to further clarify the role of p42.3 in the onset and development of colorectal cancer, this study constructed p42.3-involved colorectal cancer apoptosis regulatory network by constructing a regulatory network of early diagnosis gene maker of colorectal cancer.

GO function analysis and KEGG signal pathway analysis were performed using the gene ontology database and the Kyoto Gene and Genome Encyclopedia database for the seven gene markers screened by the Meta analysis, including WWOX, K-ras, COX-2, p53, APC, DCC and PTEN, to establish regulatory network model of colorectal cancer primary apoptosis. The results showed that DCC positively regulated the apoptotic signal pathway. It has been found in recent years that DCC is the largest human tumor suppressor gene (Kazemzadeh et al., 2015) closely related to onset and development of colorectal cancer. PTEN is an important tumor suppressor gene with phosphatase activity. It has three functions: biological process, molecular function and cellular component. It plays a role in biological processes such as T cell receptor signal pathway, phosphoinositol metabolism process and phospholipid

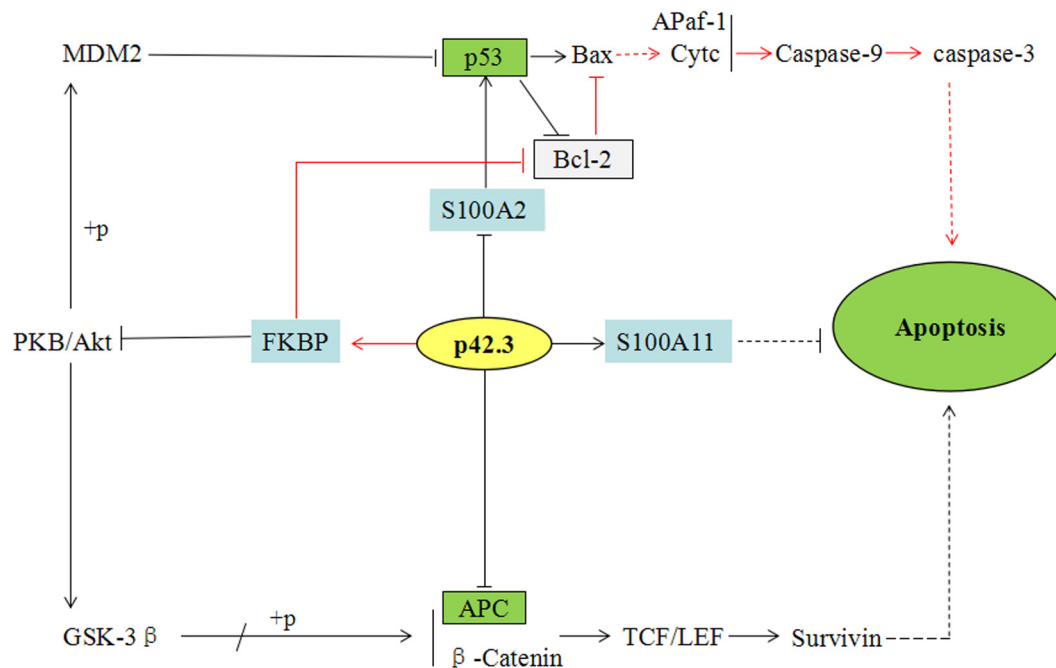


Fig. 2. Regulatory network map of colorectal cancer primary apoptosis.

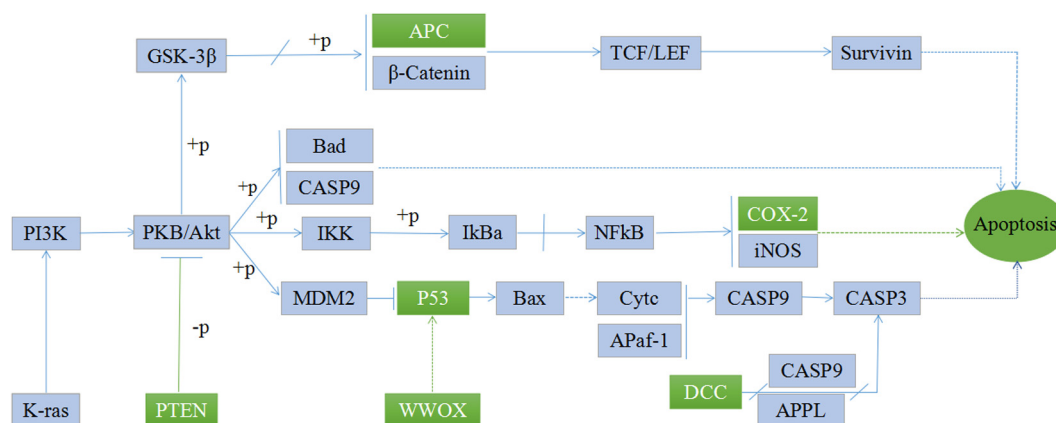


Fig. 3. Regulatory network for p42.3 involvement in colorectal cancer cell apoptosis (the red pathway indicates the possible acting pathway for p42.3 involvement in cell apoptosis).

metabolism. The colorectal cancer apoptosis regulatory network model constructed in this study revealed that PTEN could negatively regulate serine/threonine protein kinase B (PKB / Akt) and participate in the apoptotic pathways, which is consistent with the reports of Fanye et al. (2016). COX-2 is involved in biological processes such as cyclooxygenase pathway, inflammatory response and blood pressure regulation. COX-2 is an inducible enzyme called “rapid response gene”. Lowly expressed in normal tissue, its expression rapidly increases under stimulation by a variety of internal and external factors. Tabriz et al. (2016) reported that COX-2 was involved in the carcinogenesis of tumors to a great extent. p53 plays an important role in biological processes and cellular components, participates in the process of apoptosis and plays a positive regulatory role in the apoptotic signal pathway. Al-Saran et al. (2016) found that zinc can induce apoptosis of human breast cancer MCF-7 cells by up-regulating the expression of p53 and p21. Genomic data analysis found that p53 can affect the incidence of cancer (Stracquadanio et al., 2016). Both APC and WWOX have the three functions of biological processes, molecular functions and cell components. APC is involved in the process of apoptosis and has the effect of promoting apoptosis. WWOX is involved in p53-mediated apoptotic signal pathway and Wnt signal pathway. Some studies have reported that APC as a negative regulating protein of Wnt signal pathway can lead to abnormal activation of Wnt signal transduction pathway in case of insufficient expression, indicating that APC as a colorectal cancer suppressor is involved in tumor carcinogenesis of colorectal cancer (YBlundon et al., 2016; Dan et al., 2016). WWOX gene is associated with tumor infiltration degree, lymph node metastasis and clinicopathological staging. Lowly expressed in a variety of tumor cells, it can induce apoptosis of tumor cells when overexpressed (Xiong et al., 2010; Baykara et al., 2010). Recent studies have found that K-ras gene mutation is an adverse factor in onset, development and prognosis of colorectal cancer, which is closely related to treatment effect of targeted therapy. K-ras is an oncogene, and its mutation is an early event of colorectal cancer. K-ras gene is attracting more and more attention in tumor therapy. The detection of K-ras gene mutation is conducive to individualization of prior tumor therapy, which plays a very important role in the treatment of colorectal cancer (Liu and Fu, 2012; Gao et al., 2017a,b).

By combining the colorectal cancer gene marker-involved regulatory network and p42.3-involved regulatory network, p42.3-based colorectal cancer apoptosis regulatory network was constructed in this study. According to the Bayes’ theorem and conditional probability, it is predicted that p42.3 may regulate the apoptosis of colorectal cancer cells through “FKBP → Bcl-2 → Bax → caspase-9 → caspase-3”, which lays the foundation for in-

depth exploration of p42.3 action mechanism in onset and development of colorectal cancer.

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