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Basic Study

Changes in extracellular matrix in different stages of colorectal cancer and their effects on proliferation of cancer cells

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Abstract**BACKGROUND**

The extracellular matrix is the main component of the tumor microenvironment. Extracellular matrix remodels with the oncogenesis and development of tumors. Previous studies usually focused on the changes of proteins in normal colorectal tissues and colorectal cancers. Little is known about the changes in the extracellular matrix in different stages of colorectal cancer and the effects of these changes on the development of this cancer.

AIM

To test the changes of type I collagen, type IV collagen, matrix metalloproteinase-2 (MMP-2), matrix metalloproteinase-9 (MMP-9), and tissue inhibitor of metalloproteinase-3 (TIMP-3) in different stages of colorectal cancer and the effects of these changes on the proliferation of cancer cells.

METHODS

The extracellular matrix from various stages of colorectal cancer and normal colon tissue was obtained by using acellular technology. We used proteomics to detect the differential expression of proteins between normal colon tissues and colorectal cancer tissues, and then we used Western blot to observe their expression in each stage of colorectal cancer and in normal colon tissue. By co-culturing the extracellular matrix and HT29 colon cancer cells *in vivo* and *in vitro*, we tested the cancer cell proliferation rate *in vitro* by methyl thiazolyl tetrazolium (MTT) assay and *in vivo* by measuring the tumor volume.

RESULTS

The expression of type I collagen and MMP-2 increased with increased tumor stage. The expression of MMP-9 was higher in colorectal cancer tissues and was

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highest in stage III cancer. The expression of type IV collagen and TIMP-3 decreased with increased tumor stage. The proliferation rate of cancer cells in the extracellular matrix of colorectal cancer was higher than that in the extracellular matrix of the normal colon.

CONCLUSION

These data suggest that the extracellular matrix structure and composition become disorganized during the development of tumors, which is more conducive for the growth of cancer cells.

Key words: Colorectal cancer; Extracellular matrix; MMP; Proliferation; Collagen; TIMP

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Core tip: The extracellular matrix remodels during the occurrence and development of tumor. In order to study the changes of extracellular matrix, we obtained the extracellular matrix of colorectal cancer by acellular technology. We found that type I collagen, MMP-2, and MMP-9 increased in the colorectal cancer tissue, while type IV collagen and TIMP-3 decreased in the colorectal cancer tissue. Furthermore, we co-cultured the extracellular matrix and HT 29 cancer cells *in vivo* and *in vitro*, and found that the cancer extracellular matrix was more conducive for the growth of cancer cells than the normal tissue extracellular matrix.

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INTRODUCTION

With the development of the “soil-seed” theory, the effect of the tumor microenvironment on tumor cells has received more attention^[1]. The tumor microenvironment is a complex system consisting of the extracellular matrix (ECM), many types of cells, and bioactive factors, which control the complex interactions between tumor cells and stromal cells and between cells and the ECM^[2]. During tumorigenesis, the ECM plays a role of “double-edged sword” in the process of tumor proliferation and invasion^[3]. On the one hand, the ECM controls the proliferation, differentiation, and metastasis of tumor cells, and acts as a natural barrier. On the other hand, the remodeled ECM provides a loose “soil” for tumor cells to promote the occurrence and development of tumors^[4,5]. This process of remodeling occurs at the same time with tumor formation, as shown by changes in the molecular composition, amount, and structure of the ECM^[6].

The research on cell function is either in two-dimensional (2D) environment or in three-dimensional (3D) environment. Studies have shown that there are differences in cell proliferation, gene expression, and cell migration in 2D *vs* 3D cultures^[6-8]. The 3D *in vitro* experiments were better than 2D cultures in imitating tumor cell microenvironment *in vivo*. The *in vitro* 3D culture refers to tumor cells cultured in collagen, Matrigel, or fibrin^[9]. However, none of them can capture the complexity of the native matrix. The tumor ECM obtained by decellularization technology can contain almost all the proteins and their ratios in the natural tissue, which can more realistically simulate the tumor environment in which tumor cells live.

Previous studies have demonstrated that the composition of the ECM changes during cancer formation^[10,11]. However, the relationship between the stages of colorectal cancer (CRC) and the changes in the ECM and the proliferation of cancer cells is unclear. Therefore, we obtained the tumor ECM by decellularization and aimed to observe the changes in the ECM during different stages of CRC and the effects of these changes on the proliferation of cancer cells.

MATERIALS AND METHODS

Patients and tissue samples

Tissues were removed from 60 patients with CRC during surgery at Beijing Chaoyang Hospital, Capital Medical University. All procedures in this study were approved by the Medical Ethics Committee of Beijing Chaoyang Hospital, and all patients provided written informed consent. Tumor stage was classified according to the 8th edition of the American Joint Committee on Cancer TNM staging system for CRC. The patients included 34 males and 26 females and none had received preoperative chemoradiotherapy. Of these patients, 10 were classified with stage I disease, 22 with stage II, 19 with stage III, and 9 with stage IV. Ten cases with a normal colon were selected as a control group. All samples were put into the digestive solution composed of 0.25% trypsin and 0.02% EDTA and were continuously oscillated at 37 °C for 24 h at 130 rounds per minute. After that, the tissues were put into 0.5% Triton X-100 buffer and continuously oscillated at 150 rounds per minute for 24 h. Then, the ECM was obtained. After freeze-drying, the ECM samples were sterilized by Co-60 radiation and stored at -20 °C.

Western blot analysis

Western blot assays were performed to detect the protein level. The protein concentrations were tested with a BCA Protein Assay Kit (Pierce, United States). Equal amounts of protein (20 µg) were loaded. Type I collagen, type IV collagen, MMP-2, MMP-9, and TIMP-3 antibodies were purchased from Beijing Biosynthesis Biotechnology Co, LTD. All primary antibodies were used at a 1:1000 dilution. The enhanced chemiluminescence reaction was used to detect the protein bands.

Co-culture of cells and the extracellular matrix

The sterilized ECM was cut into 3 mm × 3 mm × 3 mm pieces under aseptic conditions and placed in a 96-well culture plate. One hundred microliter of colon cancer HT29 cells at a density of 1×10⁶ cells/mL (1×10⁵ cells) was slowly added vertically into the ECM, and then cultured in an incubator containing 5% CO₂.

Methyl thiazolyl tetrazolium assay

The culture medium in the 96-well plate was removed and treated with methyl thiazolyl tetrazolium (MTT) solution for 4 h. After removing the supernatant, 150 µL of DMSO was added to dissolve the tetrazolium salt and measure the optical density using a Multiskan Spectrum Microplate Reader (Thermo Labsystems, Milan, Italy) at 570 nm. The experiment was repeated three times.

Animal experiments

Six-week-old male nude BALB/c mice were randomly divided into five groups with 10 mice in each group. The density of colon cancer HT29 cells was adjusted to 1 × 10⁶ cells/mL. The ECM from each group was cut into 3 mm × 3 mm × 3 mm pieces under aseptic conditions and placed in a 96-well plate. In each well, 50 µL of the above cell suspension (5×10⁴ cells) was slowly added and allowed to stand for 1 h. Abdominal anesthesia was performed with 10% chloral hydrate (0.01 g/mL), and the right forearm underarm skin in each mouse was cut under aseptic conditions, and the ECM and cancer cell complex were embedded subcutaneously. The animals were killed on the 30th day, and the long diameter (a) and short diameter (b) of the tumor were measured with a Vernier caliper. Approximate tumor volume was obtained using the following equation: $V = a \times b \times b/2$.

All animals were housed under a 12/12 h light/dark cycle at 22 °C and 40%-60% relative humidity conditions. They were given free access to water and food. All animal experimental protocols were done according to the Principles of Laboratory Animal Care and the Guide for the Care and Use of Laboratory Animals, published by the National Science Council, China.

Statistical analysis

Statistical analyses were carried out using the Statistical Package for the Social Sciences version 22.0 and figures were made by GraphPad Prism 6.0. All data are expressed as the mean ± SD. Statistical analyses were performed by means of *t*-tests when two groups were compared or one-way ANOVA when more than two groups. Statistical significance was set at $P < 0.05$.

RESULTS

Preparation of extracellular matrix

An overview of ECM preparation is provided in [Figure 1](#). The normal tissue ECM and CRC ECM were obtained by decellularization. From outward appearance, there was no obvious difference in normal tissue ECM and CRC ECM. All of them presented milk white, sticky surface and soft texture.

High expression of type I collagen, MMP-2, and MMP-9 and low expression of type IV collagen and TIMP-3 in extracellular matrix of colorectal cancer

We used proteomics to analyze the differential expression of proteins in normal colorectal tissue and colorectal cancer tissue, and some of them were selected for analysis in each stage of colorectal cancer ([Table 1](#)). The expression of type I collagen was highest in stage III and stage IV and lowest in normal tissue and stage I. Spearman correlation analysis showed that the expression of type I collagen was positively correlated with the stage of CRC ([Figure 2](#)). The expression of MMP-2 was higher in the colorectal cancer tissues and it increased with the increased tumor stage. The expression of MMP-9 was higher in the colorectal cancer tissue, but it was highest in the stage III CRC ([Figure 3](#)). However, the expression of type IV collagen and TIMP-3 gradually decreased with increased CRC stage. Spearman correlation analysis showed that type IV collagen was negatively correlated with the stage of CRC ([Figures 2 and 3](#)).

Extracellular matrix of colorectal cancer is conducive to the proliferation of tumor cells *in vitro* and *in vivo*

To study the growth of cancer cells in each group, we co-cultured cancer cells and ECM *in vivo* and *in vitro*. The proliferation of cancer cells was determined *in vitro* by the MTT assay. We found that cancer cells co-cultured with CRC ECM grew significantly better than cancer cells with normal tissue ECM ([Figure 4](#)). *In vivo* tumor volume in each group was larger and was greatest in stage IV CRC ECM. Compared to the normal tissue ECM, the CRC ECM was more conducive to the proliferation of cancer cells ([Figure 5](#)).

DISCUSSION

The occurrence of malignant tumors is a complex process of interactions between cancer cells and the tumor microenvironment^[12,13]. Paget described the relationship between cancer cells and the tumor microenvironment as the seed and soil, indicating that the tumor microenvironment is very important for tumorigenesis and tumor progression^[14]. The tumor microenvironment is a unique environment that emerges during the course of tumor progression^[12,15]. The tumor microenvironment is composed of ECM, cells, and interstitial fluids, and the ECM is the major component^[16]. During cancer progression, the structure and composition of the ECM become disorganized, and this change can promote cellular transformation and metastasis^[4,16,17].

Collagen is an important component of the ECM and is considered a structural barrier against tumor invasion^[18,19]. Paradoxically, increased expression of collagen is associated with an elevated incidence of proliferation and invasion^[20,21]. Abnormal expression of collagens and pathological collagen crosslinking ultimately resulted in increased tissue stiffness and altered tissue homeostasis^[6]. The stiff ECM affects many aspects of the cell, such as motility, proliferation, and chemotherapeutic drug efficiency^[22,23]. In our study, we found increased expression of type I collagen and decreased expression of type IV collagen in the ECM of CRC. The imbalance of ECM composition could result in an increase in ECM stiffness, which provides enough traction for cell proliferation and migration^[24].

MMP-2 and MMP-9 are members of the MMP family, and they play an important role in the degradation and remodeling of the ECM^[25]. TIMP-3 exists only in the ECM and could inactivate the MMPs by binding to MMPs^[26]. Thus, reaching a balance between TIMPs and MMPs is conducive to the stability of the ECM. The remodeled ECM affects the motility and proliferation of cancer cells^[22]. In our study, we found that the expression of MMP-2 and MMP-9 was higher in CRC tissue than in the normal tissue. The expression of MMP-2 increased with increased tumor stage. The expression of MMP9 was highest in stage III and we speculated that this is associated with the deactivation of MMP9.

In conclusion, our study showed that the expression of type I collagen, MMP-2, and MMP-9 increases in CRC while the expression of type IV collagen and TIMP-3



Figure 1 Overview of extracellular matrix preparation. A: Normal human colon tissue; B: Human colorectal cancer tissue; C: Normal human colon tissue or human colorectal cancer tissue were decellularized and shown in a glass culture dish.

decreases in this malignancy. The changes in the composition of the ECM are conducive to cell proliferation. Thus, these findings will provide a new platform for the future design of anticancer drugs based on the biophysical properties of the tumor microenvironment.

Table 1 Analysis of differential expression of proteins in normal colorectal tissues and colorectal cancer tissues

Protein	Description	T vs N fold-change	Regulated type	P value
A0A024R6R4	MMP2	1.2683	Up-regulated	0.042
P14780	MMP9	1.3930	Up-regulated	0.031
P35625	TIMP3	0.5057	Down-regulated	0.026
P02462	Collagen IV	0.4551	Down-regulated	0.049
P02452	Collagen I	1.9724	Up-regulated	0.018

N: Normal colorectal tissues; T: Colorectal cancer tissues. Statistically significant ($P < 0.05$).

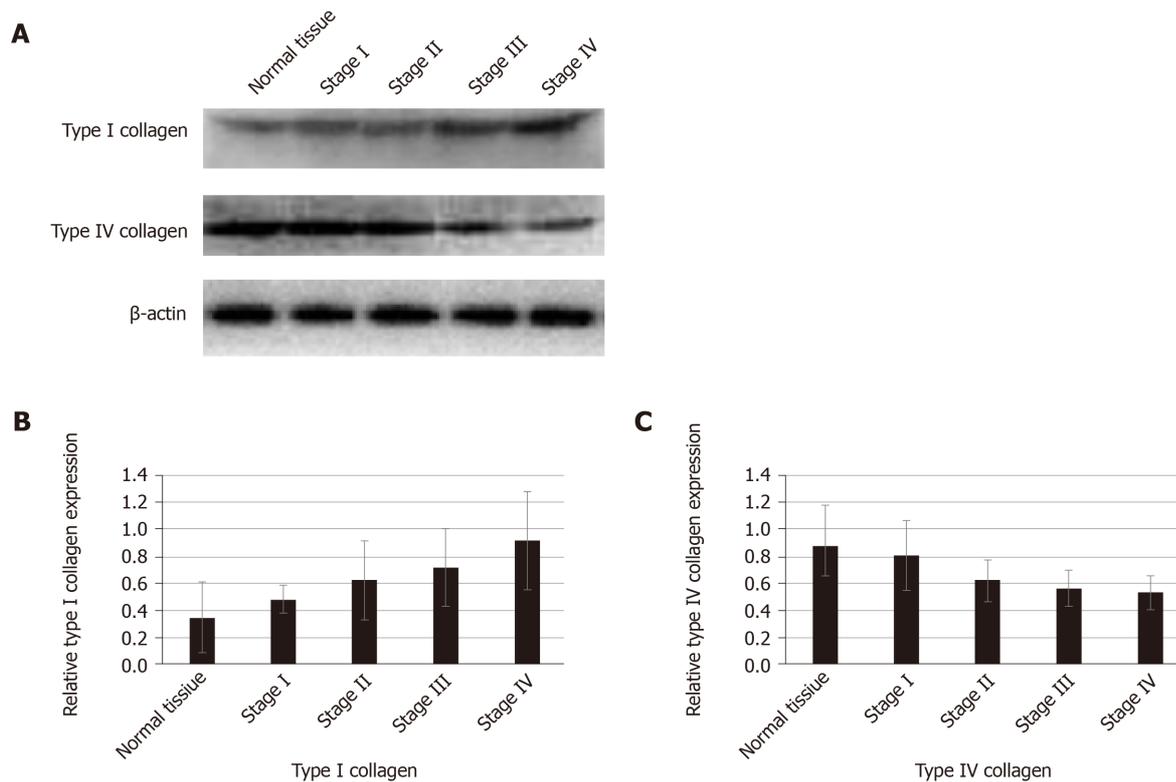


Figure 2 Expression of type I collagen and type IV collagen in normal tissue and colorectal cancer. A: Western blot showing the expression of type I collagen and type IV collagen; B: The expression of type I collagen in the extracellular matrix (ECM) of stages III and IV colorectal cancer was highest. In the ECM of stages I and II colorectal cancer, the expression was relatively low. The expression of type I collagen was positively associated with the stage of colorectal cancer ($r = 0.706$, $P < 0.01$); C: The expression of type IV collagen was negatively correlated with the stage of colorectal cancer ($r = -0.796$, $P < 0.01$).

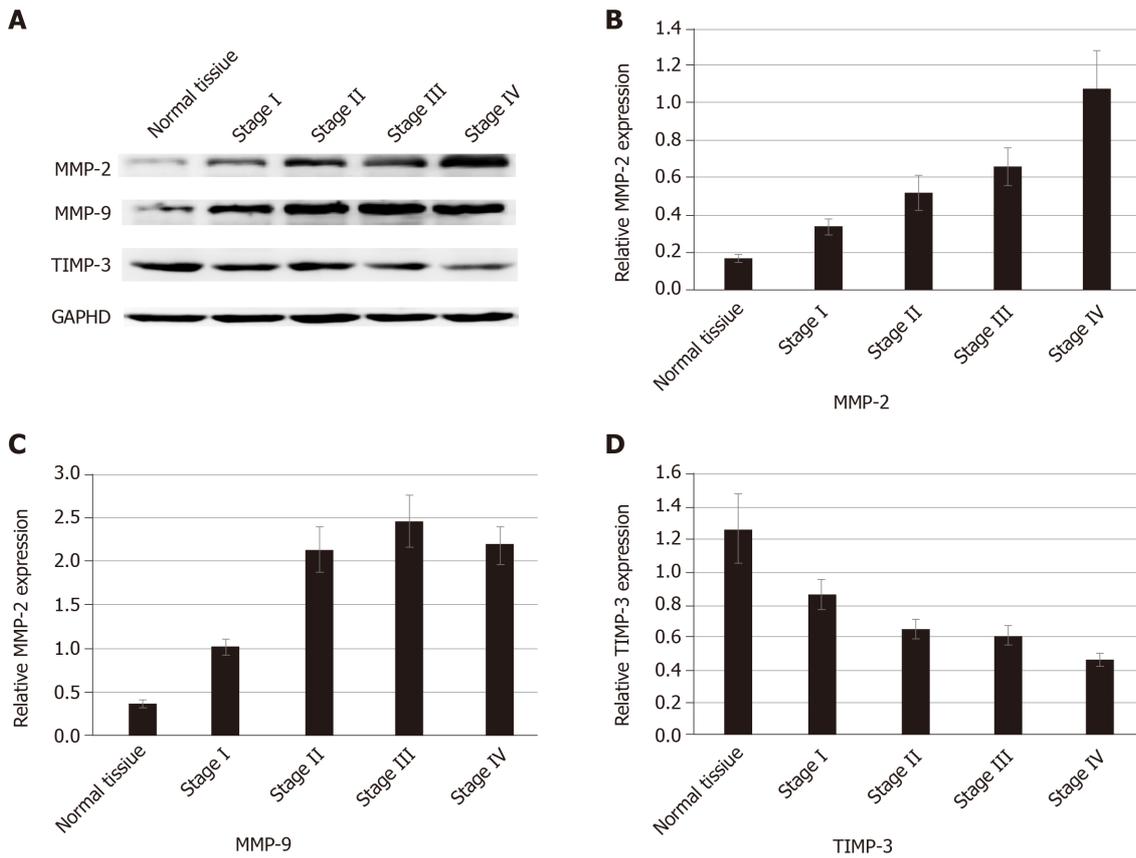


Figure 3 Expression of MMP-2, MMP-9, and TIMP-3 in normal tissue and colorectal cancer. A: Western blot showing up-regulated expression of MMP-2 and MMP-9 and down-regulated expression of TIMP-3 in colorectal tissues; B: The expression of MMP-2 increased with increased tumor stage; C: The expression of MMP-9 in the colorectal cancer tissues was higher than that in the normal tissue and it was highest in the stage III colorectal cancer; D: The expression of TIMP-3 decreased with increased tumor stage.

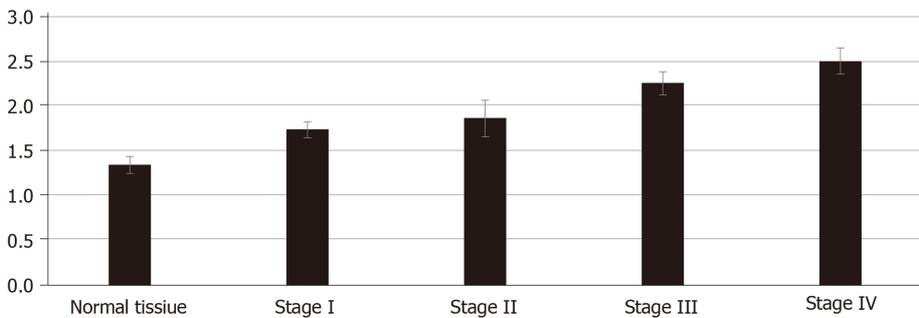


Figure 4 Cancer cells co-cultured with colorectal cancer extracellular matrix and normal tissue extracellular matrix *in vitro*. Compared to the optical density (OD) value of the normal tissue extracellular matrix (ECM), the OD value of colorectal cancer (CRC) ECM was higher. When comparing every two OD values of the CRC ECM, the difference between stage I ECM and stage II ECM was not statistically significant ($P = 0.138$).

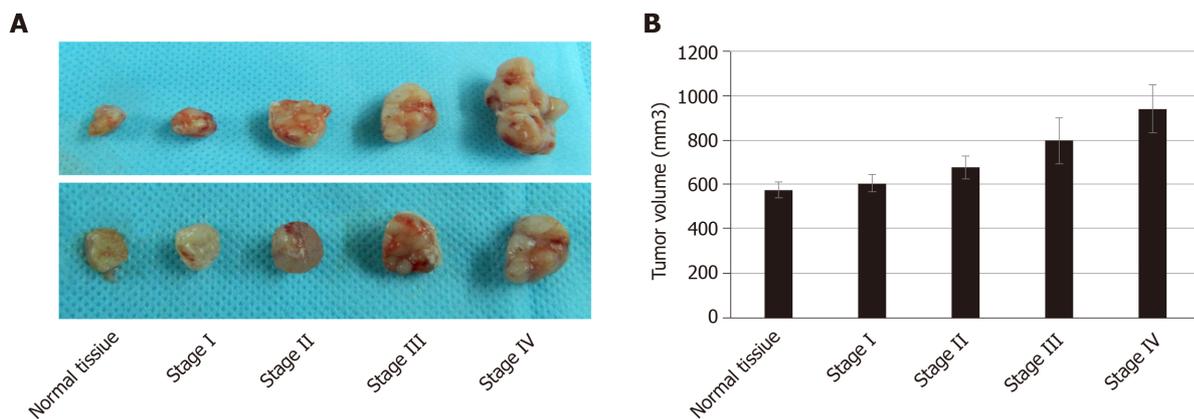


Figure 5 Cancer cells co-cultured with colorectal cancer extracellular matrix and normal tissue extracellular matrix *in vivo*. A: The volume of tumor in colorectal cancer extracellular matrix (ECM) was bigger than that in the normal tissue ECM; B: When comparing every two tumor volumes, the differences between stage I ECM and normal tissue ECM and between stage I ECM and stage II ECM were not statistically significant ($P = 0.526$ and 0.152 , respectively).

ARTICLE HIGHLIGHTS

Research background

The extracellular matrix is not only the substantial support for tumor cells but also promotes the occurrence and development of tumors.

Research motivation

The extracellular matrix changes in the structure and composition during the process of oncogenesis and development of tumors. However, little is known about the changes of the extracellular matrix in different stages of colorectal cancers and the effect of these changes on the development of colorectal cancer. The answer to this may provide a new platform for the future design of anticancer drugs.

Research objectives

In this study, the authors aimed to study the changes of the extracellular matrix in different stages of colorectal cancer and the relationship between the changes of the extracellular matrix with the proliferation of cancer cells.

Research methods

The extracellular matrix was obtained by acellular technology from 60 colorectal cancer patients. Type I collagen, type IV collagen, MMP-2, MMP-9, and TIMP-3 were analyzed by Western blot. Besides, the extracellular matrix and the cancer cells were co-cultured *in vivo* and *in vitro* to study the effect of the extracellular matrix on the cancer cell proliferation.

Research results

The expression of type I collagen, MMP-2, and MMP-9 increased with increased tumor stage. The expression of type IV collagen and TIMP-3 decreased with increased tumor stage. The changed extracellular matrix promotes the cancer cell proliferation.

Research conclusions

This study showed that the extracellular matrix plays an important role in the development of tumor and this provides a certain theoretical basis for anti-tumor therapy.

Research perspectives

The tumor microenvironment is a complex system. The extracellular matrix obtained by decellularization provides an ideal tumor model to study the occurrence and development of tumor.

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