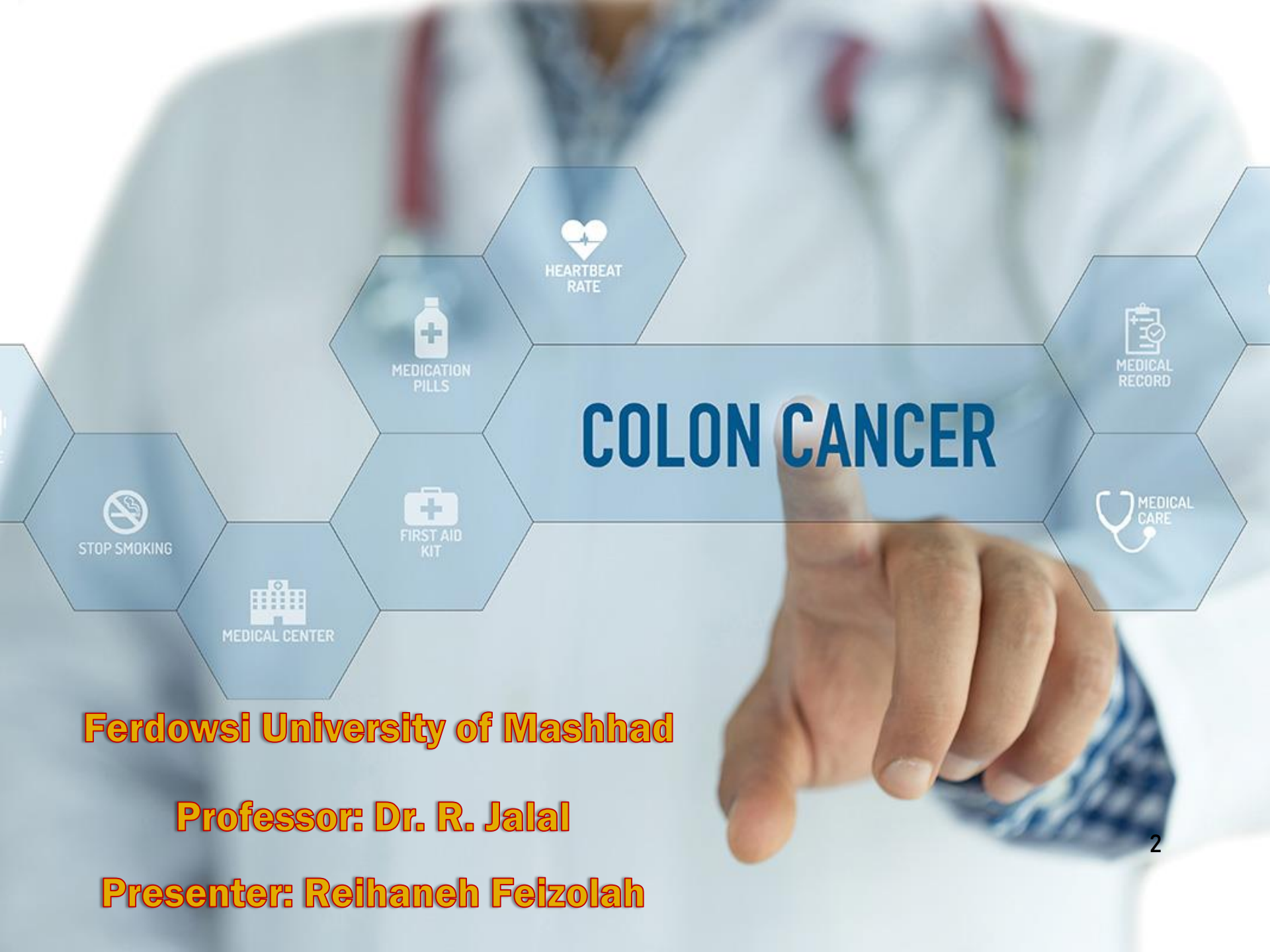


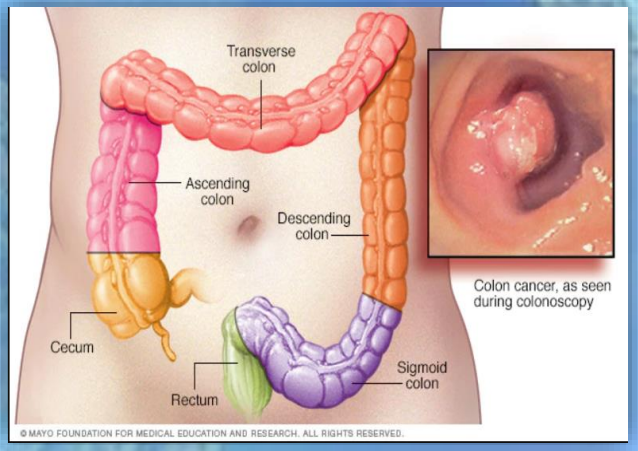

Ferdowsi University of Mashhad

Professor: Dr. R. Jalal

Presenter: Reihaneh Feizolah

# Overview

- ✓ Colorectal cancer (CRC), also known as bowel cancer, colon cancer, or rectal cancer
- ✓ Colon cancer is the fourth cause of mortality at the world
- ✓ More than 940,000 cases occur annually worldwide, and nearly 500,000 die from it each year.
- ✓ Caused by abnormal growth of cells
- ✓ Surgery is considered the primary therapeutic
- ✓ Altered metabolism has been recognized as a common hallmark of cancer



# Risk Factor

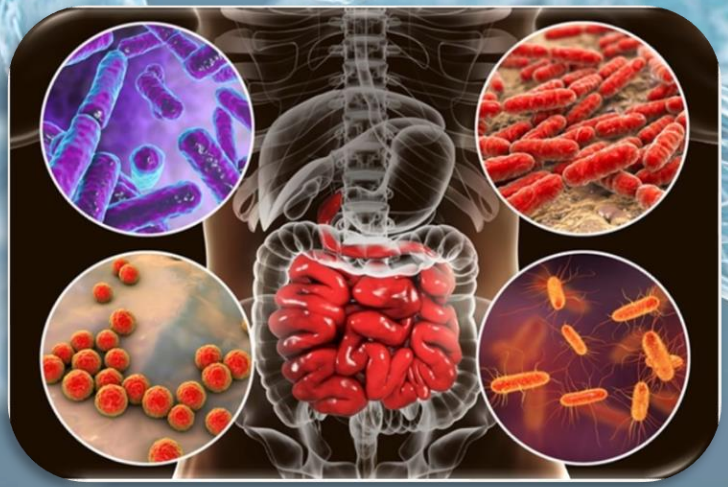
- ✓ Smoking
- ✓ Heavy consumption of alcohol
- ✓ Overweight and obesity
- ✓ Physical inactivity
- ✓ High consumption of red and processed meat
- ✓ Low consumption of dietary fiber, whole grains, healthful nutrients
- ✓ Inherited in only 5% of cases: Lynch Syndrome

# Protective Factor

- ✓ Regular physical activity
- ✓ Diet rich in fruits, vegetables, high fiber, omega 3, omega 6
- ✓ Vitamins: Vitamin D, Vitamin B6 , Folate
- ✓ Calcium and Magnesium intake


# Microbiome

- ✓ Changes in the intestinal microbiome allow environmental risk factors to initiate and promote CRC
- ✓ Changes in the gut microbiome occur during early stages of colorectal carcinogenesis
- ✓ As biomarkers for early detection of CRC
- ✓ Dysbiosis :pathogenic changes in microbiome profile and functions
- ✓ Association of periodontal disease with CRC risk

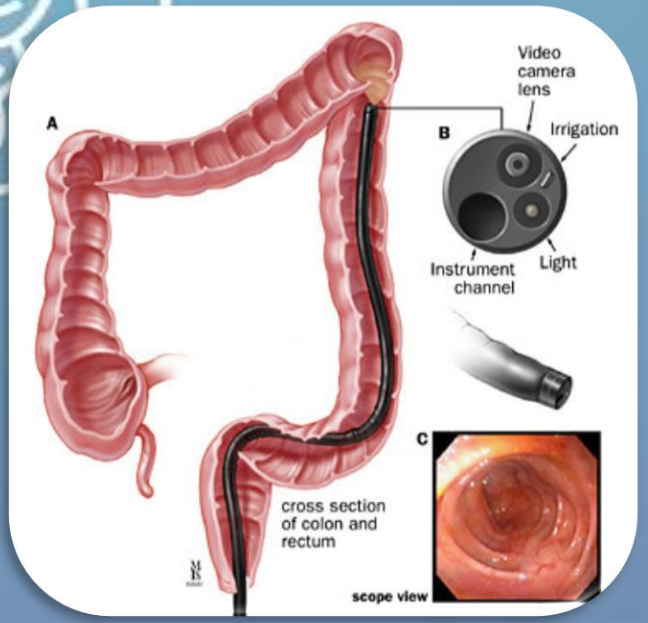


# Clinical Presentation

- ✓ Change in bowel habits, hematochezia from rectal bleeding, Iron deficiency anemia, abdominal pain, loss of weight and loss of appetite
- ✓ Metastasis occurs by lymphatic spread, hematogenous spread, contiguous or transperitoneal spread.

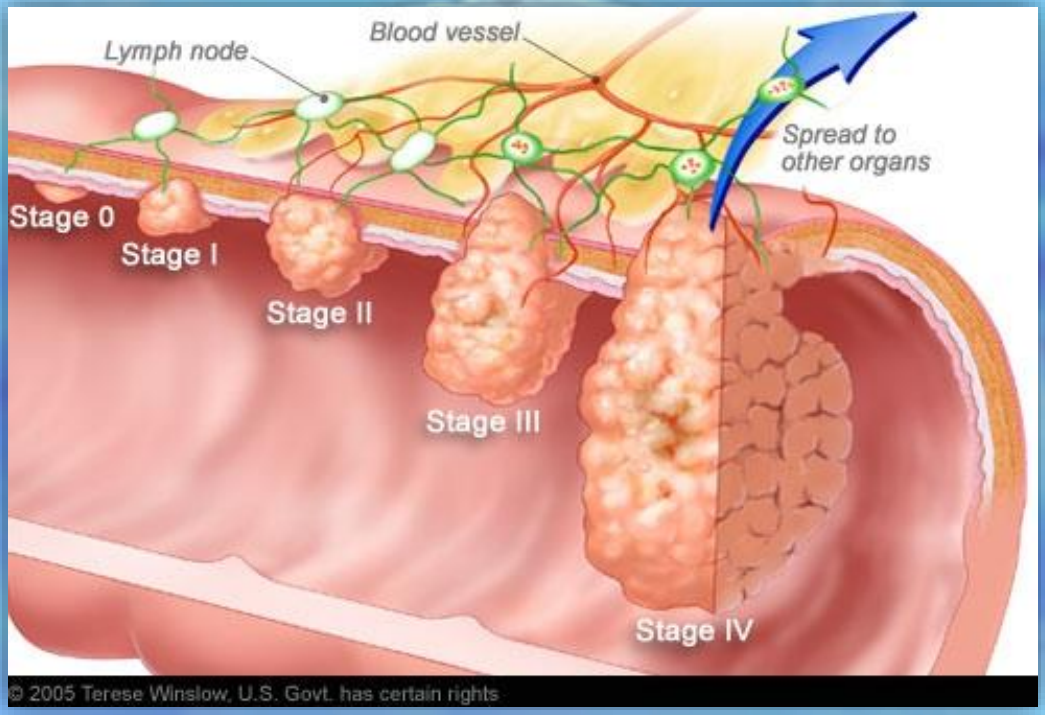
# Diagnosis

- ✓ Early stage colorectal cancers are commonly diagnosed by routine colonoscopies
- ✓ CT imaging of chest, abdomen and pelvis with contrast is needed for staging patient's CRC
- ✓ Carcinoembryonic antigen (CEA)

# Colorectal Cancer Staging

- ✓ TNM classification system:Primary **Tumor** size (T), regional lymph **Node** (N) and distant **Metastasis** (M)




Stage 0 –only in the innermost lining Stage I –has not spread beyond the inner wall
Stage II –has spread into the muscle layer
Stage III –has spread to at least one lymph node in the area.
Stage IV –has spread to distant sites in the body, such as the bones, liver, or lungs

# Glucose Metabolism in Colon Cancer

Molecular Therapy
Nucleic Acids
Original Article

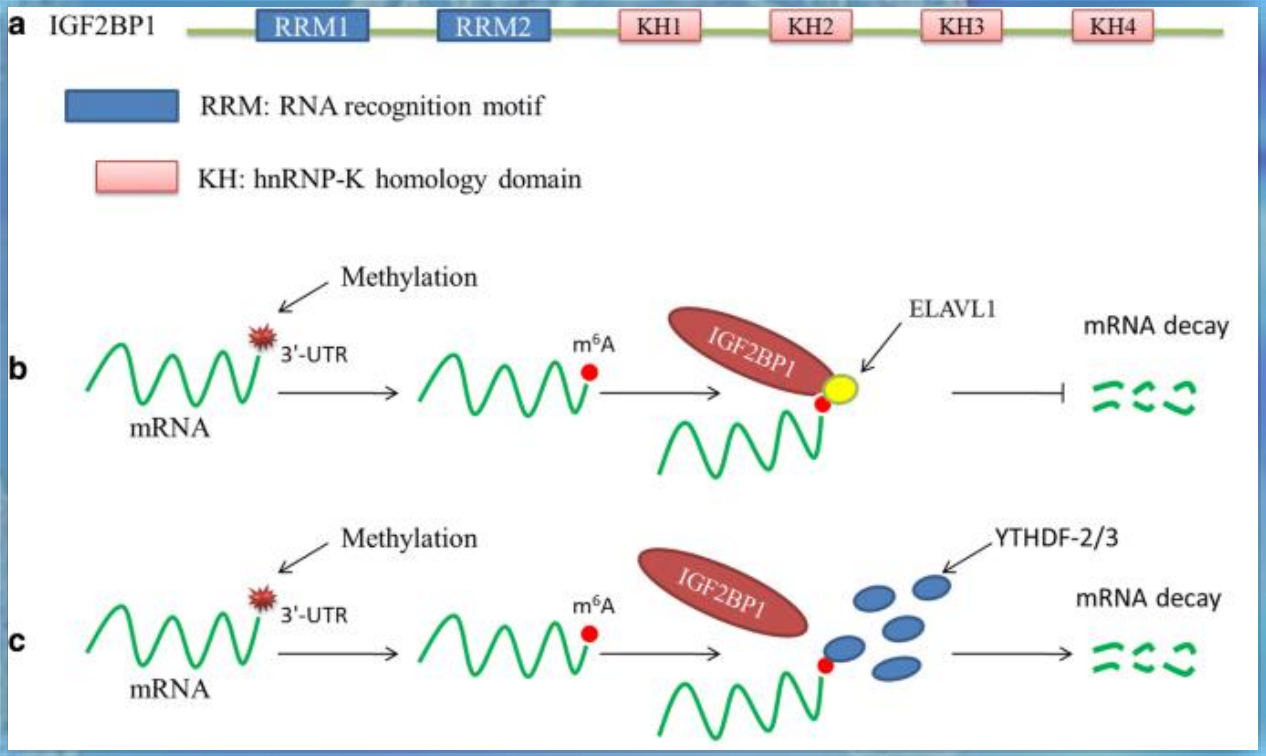
# Blocking the IGF2BP1-promoted glucose metabolism of colon cancer cells via direct de-stabilizing mRNA of the LDHA enhances anticancer effects

Xiang-liang Zhang,[1,2] Ke-jun Li,[1,2] Jin-xin Feng,[1,2] Gao-jie Liu,[1] and Yan-lin Feng[1]

[1]Department of Abdominal Surgery, Affiliated Cancer Hospital & Institute of Guangzhou Medical University, Hengzhigang Road #78, Guangzhou 510095, Guangdong, China

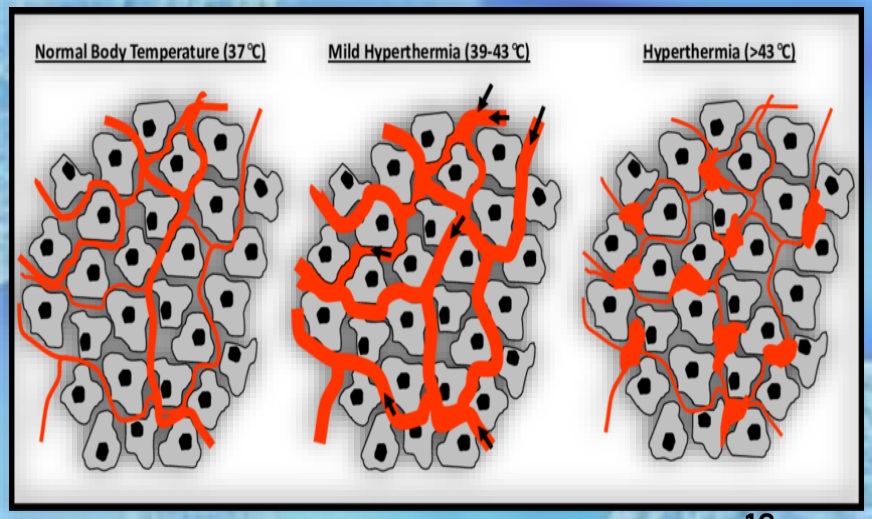
# IGF2BP1

- ✓ IGF2BP1 :Insulin-like growth factor-2 mRNA-binding protein1
- ✓ Consists of six canonical RNA-binding domains
- ✓ N6-methyladenosine (m6A)
- ✓ YT521-B homology (YTH) domain-containing proteins (YTHDFs)

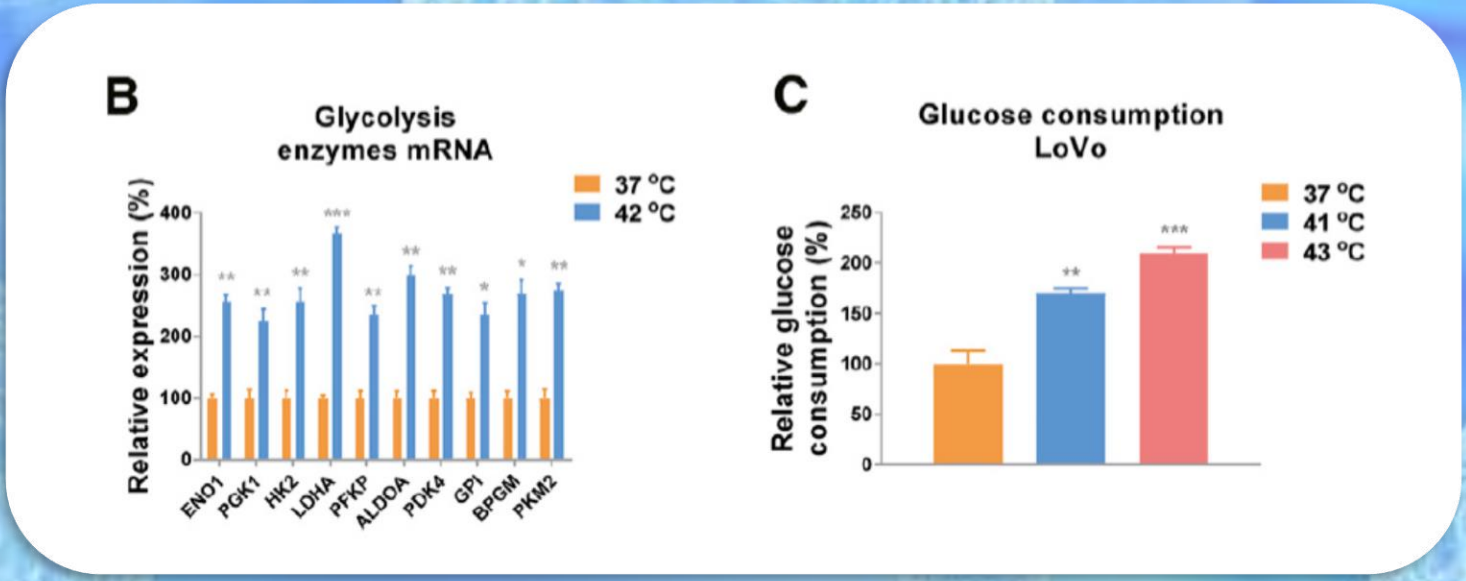


# Hyperthermia (HT)

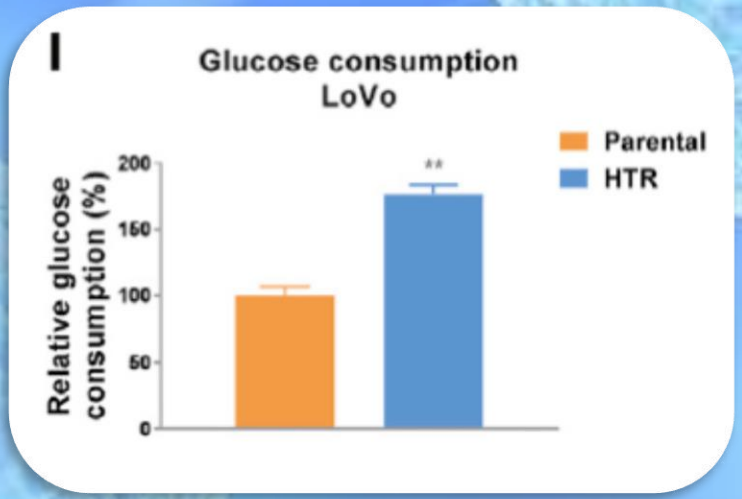
- ✓ Hyperthermia refers to raising the temperature of the whole body or local tumor tissue
- ✓ Hyperthermia is often used in combination with chemotherapy and radiotherapy for cancer treatment
- ✓ Mild hyperthermia elevates the tumor temperature within the range of 39C–45C
- ✓ At temperatures above 42°C, the tumor vasculature is directly damaged by increased permeability,. Inhibit tumor growth and metastasis.

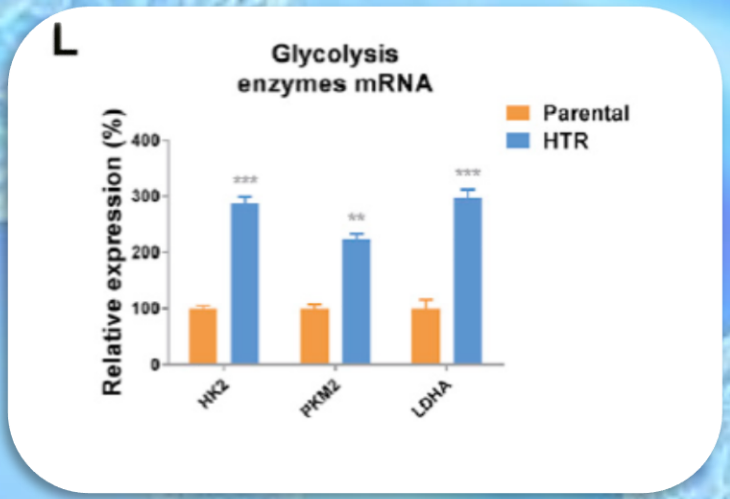


- ✓ Warburg effect: conversion of glucose to lactate, even in the presence of adequate oxygen.
- ✓ Mild HT treatment accelerated glucose metabolism and induced oxidative stress
- ✓ Blocking the HT-promoted anerobic glycolysis might be an effective approach against tumors.
- ✓ Hexokinase2 (HK2), Pyruvate kinase (PKM2) and Lactate dehydrogenase-A (LDHA) were apparently elevated under hyperthermic conditions.

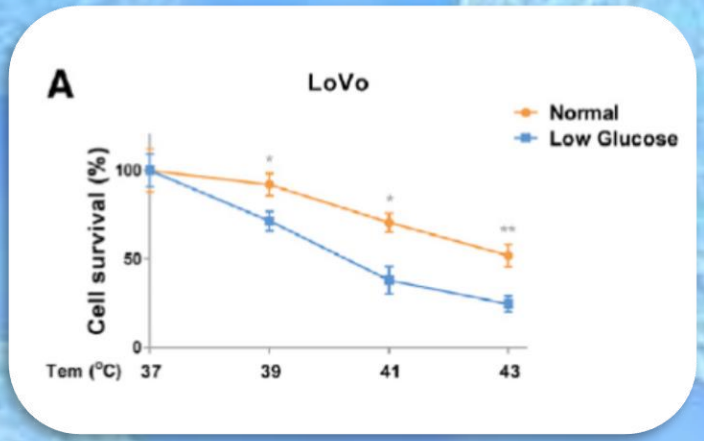


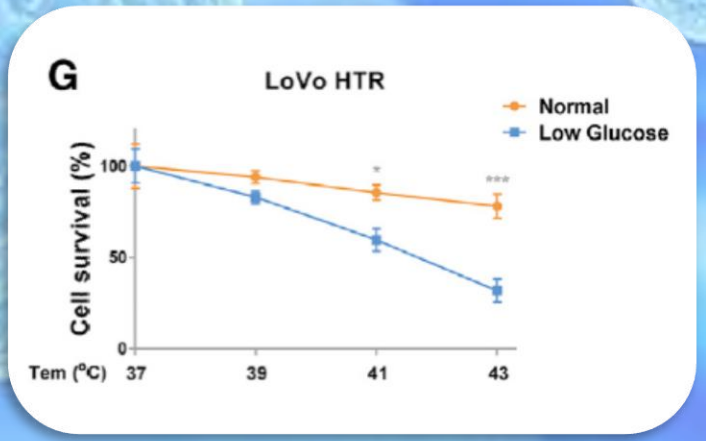
- ✓ Established a HT-resistant colon cancer cell line (LoVo HTR) via exposing cells to elevated high temperature.
- ✓ The acquired HT-resistant cells could tolerate higher temperatures compared with LoVo parental cells.
- ✓ HT-resistant cells showed significantly increased glucose consumption and glycolysis key enzyme expressions.



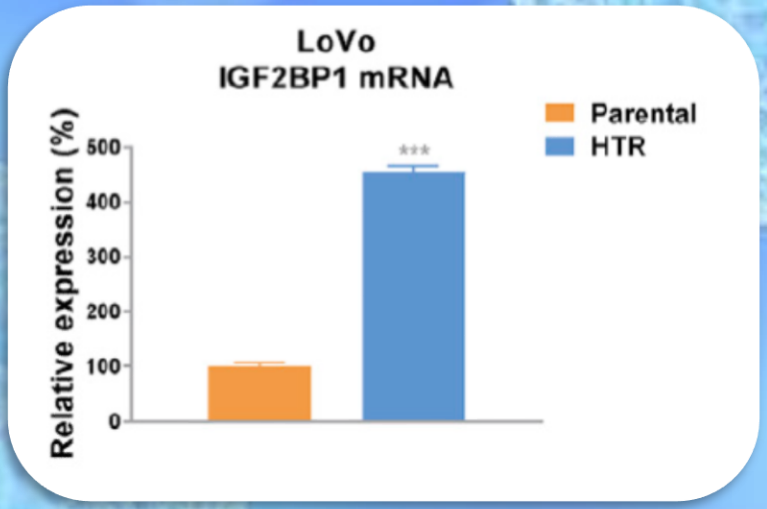



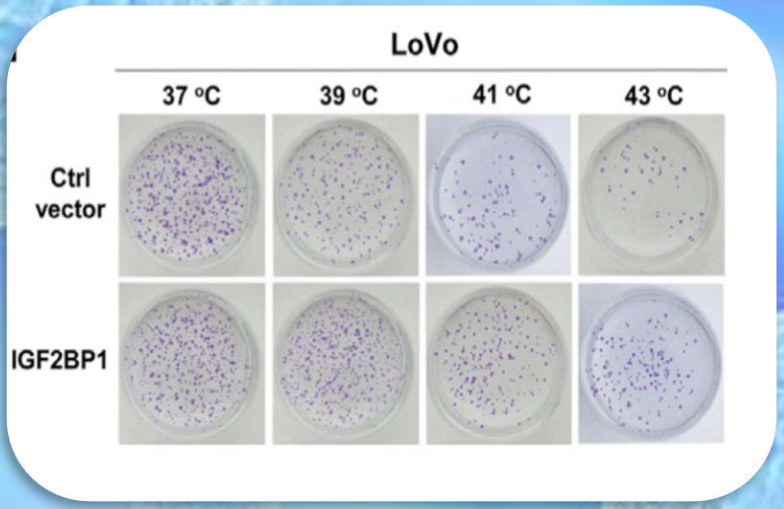
- ✓ Under low-glucose supply, colon cancer cells displayed more sensitivity to HT treatments
- ✓ LoVo HTR cells with glycolysis key enzyme silencing and inhibitor treatment displayed significantly increased cell death rate with HT treatments

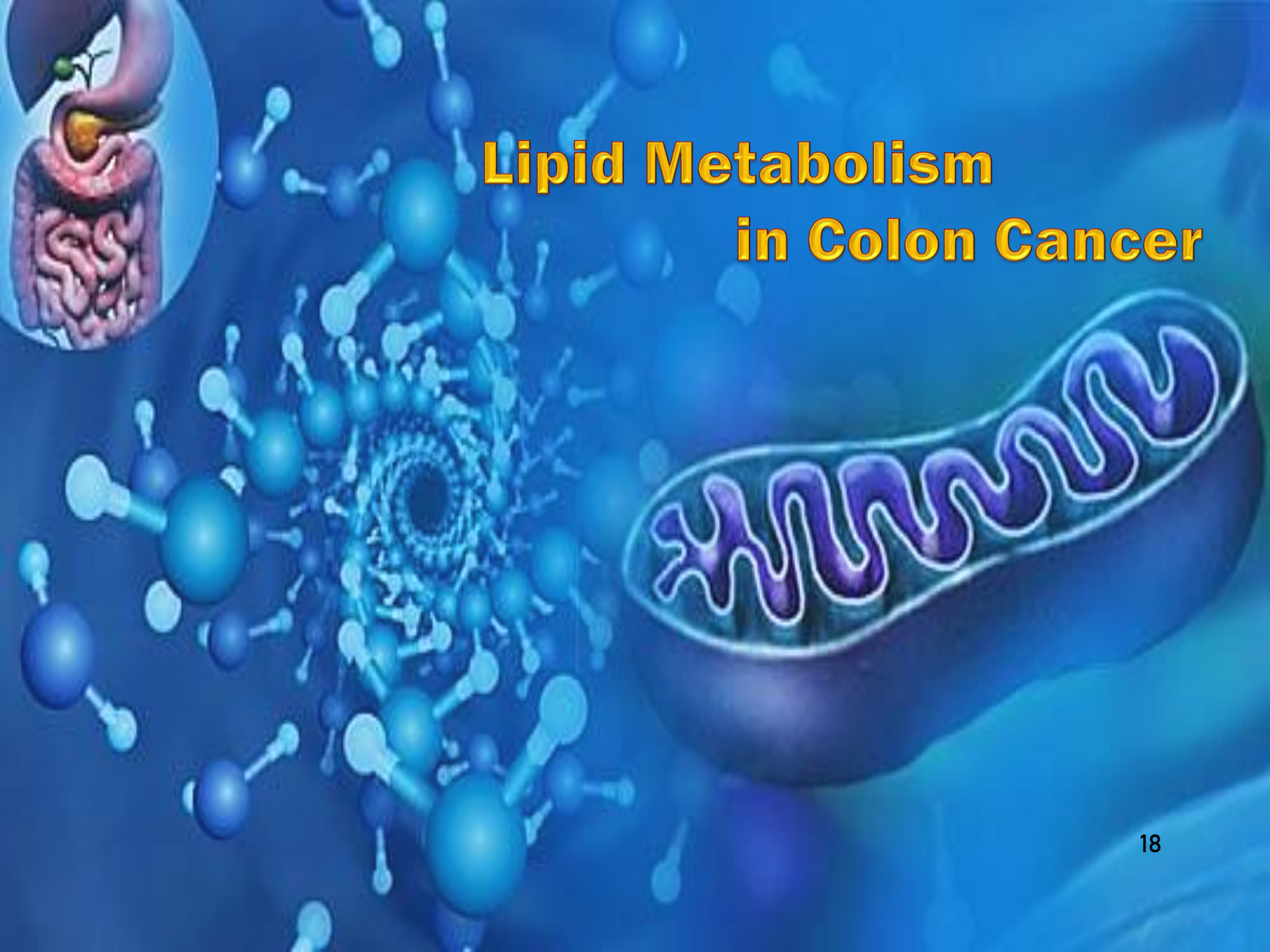


- ✓ IGF2BP1 functions as an oncogene to de-sensitize colon cancer cells to HT
- ✓ mRNA and protein expressions of IGF2BP1 were significantly upregulated in LoVo HTR cells
- ✓ Under HT, IGF2BP1 mRNA was remarkedly elevated in colon cancer cells
- ✓ IGF2BP1 upregulated LDHA expression through direct bind to 30 UTR of LDHA, leading to stabilization of LDHA mRNA.
- ✓ Silencing IGF2BP1 by shRNA effectively overrode the resistance of HTR cells from both in vitro and in vivo models.
- ✓ The regulatory mechanisms for the HT-mediated cancer cell apoptosis have not been fully understood.




Lipid Metabolism
in Colon Cancer

Xiong et al. *Cell Death and Disease* (2020)11:736
https://doi.org/10.1038/s41419-020-02936-6

Cell Death & Disease

ARTICLE Open Access

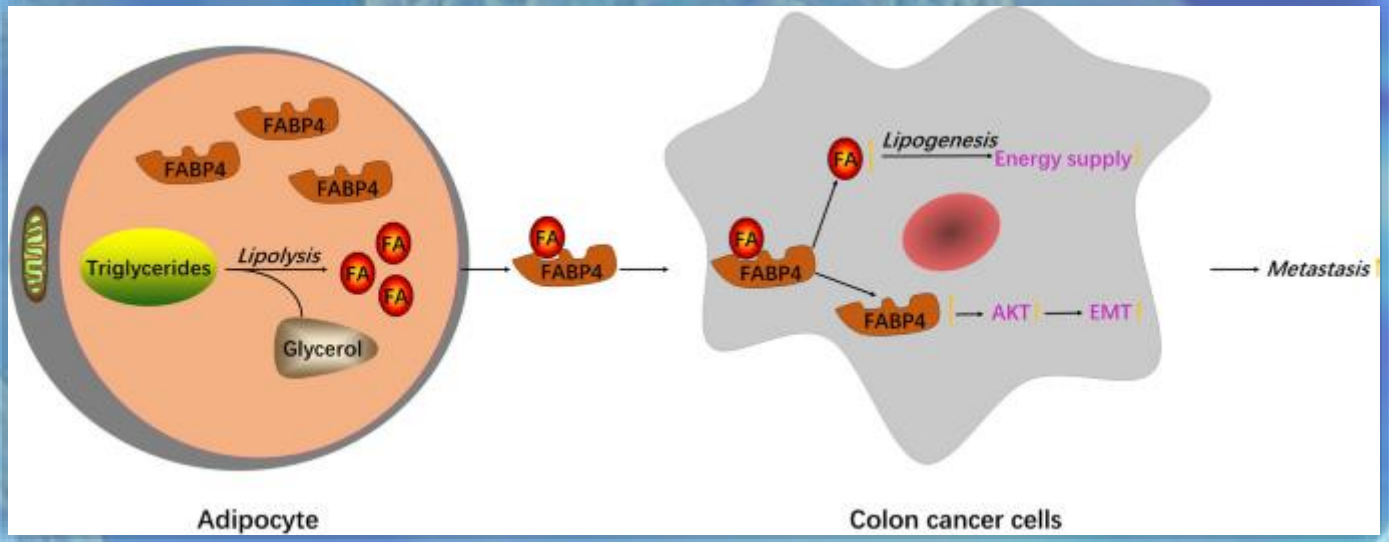
# Upregulation of CPT1A is essential for the tumor-promoting effect of adipocytes in colon cancer

Xiaopeng Xiong[1], Yang-An Wen[1], Rachelle Fairchild[1], Yekaterina Y. Zaytseva[2], Heidi L. Weiss[1], B. Mark Evers[1,3] and Tianyan Gao[1,4]

**Abstract**

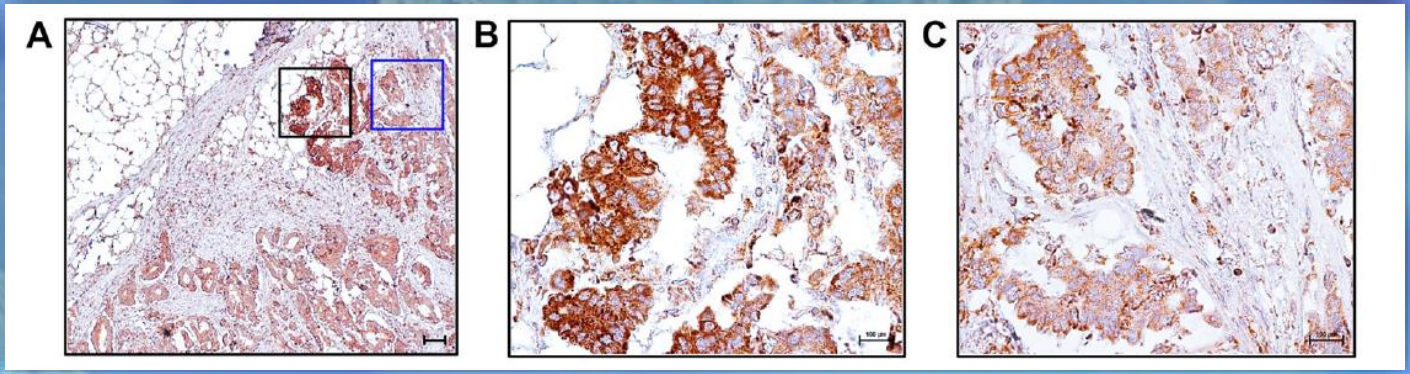
Colon tumors grow in an adipose tissue-enriched microenvironment. Locally advanced colon cancers often invade into surrounding adipose tissue with a direct contact with adipocytes. We have previously shown that adipocytes promote tumor growth by modulating cellular metabolism. Here we demonstrate that carnitine palmitoyltransferase I (CPT1A), a key enzyme controlling fatty acid oxidation (FAO), was upregulated in colon cancer cells upon exposure to adipocytes or fatty acids. In addition, CPT1A expression was increased in invasive tumor cells within the adipose tissue compared to tumors without direct contact with adipocytes. Silencing CPT1A abolished the protective effect provided by fatty acids against nutrient deprivation and reduced tumor organoid formation in 3D culture and the expression of genes associated with cancer stem cells downstream of Wnt/β-catenin. Mechanistically, CPT1A-dependent FAO promoted the acetylation and nuclear translocation of β-catenin. Furthermore, knockdown of CPT1A blocked the tumor-promoting effect of adipocytes in vivo and inhibited xenograft tumor initiation. Taken together, our findings identify CPT1A-depedent FAO as an essential metabolic pathway that enables the interaction between adipocytes and colon cancer cells.

- ✓ Advanced colon cancers often invade into surrounding adipose tissue with a direct contact with adipocytes
- ✓ Metastatic colon cancer cells often encounter adipocytes as they first disseminate
- ✓ Lipids produced in adipocytes can be transferred to cancer cells to promote tumor growth
- ✓ Cancer cells stimulates the release of fatty acids by promoting lipolysis in adipocytes




➢ Tian et al. Cancer Cell Int (2020) 20:512

- ✓ CPT1A expression was increased in invasive tumor cells within the adipose tissue
- ✓ Uptake of fatty acids renders colon cancer cells resistant to nutrient deprivation and this acquired survival advantage relies on CPT1A mediated FAO
- ✓ Uptake of fatty acids promotes the expression of CPT1A through the activation of PPARδ.
- ✓ Silencing CPT1A expression in colon cancer cells blocks the cell survival advantage provided by adipocytes



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THANK YOU