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The 15th OESO World Conference for Esophageal Diseases

November 6th-10th, 2019
China National Convention Center, Beijing, China

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PROGRAM AGENDA

November 6th-10th, 2019
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WELCOME SPEECH

Dear Colleagues,

After the "14th OESO World Congress for Diseases of the Esophagus" in Geneva, Switzerland in September 2017, the 15th OESO World Congress for Diseases of the Esophagus will be held on November 7th-10th, 2019 in China National Conference Center, Beijing, China.

As the executive president of this congress, on behalf of the "World Organization for Specialized Study on Diseases of the Esophagus(OESO)", it is my great honor and pleasure to invite you to participate the "15th OESO World Congress for Disease of the Esophagus" in Beijing, China. It will be held together by OESO, Cancer Foundation of China, China National Cancer Center, Committee of Esophageal Cancer, Committee of Epidemiology, Committee of Etiology and Committee of Endoscopy from China Anti-Cancer Association (CACA) and the Chinese Society for Diseases of the Esophagus (CSDE).

The OESO is a multi-disciplinary international organization focused on esophageal diseases. Its biennial congress aims to bring together all specialists from all over the world working in the fields of clinical management and basic research for the patients with esophageal diseases. It also provides the training courses for the trainee and programs of visiting scholar working in the field of esophageal diseases.

The 15th OESO World Congress held in Beijing, China will focus on the "Global Perspective and Novel Technology for Diseases of the Esophagus", and will provide an excellent platform for sharing not only the updated clinical management but also the scientific knowledge on diseases of the Esophagus.

Beijing is an ancient but also a beautiful modern capital city with thousand years of history and rich cultural as well as architectural heritage. Very convenient air and ground transportation will take you to any scenic spots where you wish to visit in Beijing and other places in China. You can enjoy Chinese cuisines and the beauty of operas as well as academic exchanges in this congress.

We are looking forward to meeting you in Beijing.

Jia Hu, M.D, Ph.D
Executive President of 15th OESO World Congress

WELCOME SPEECH

Dear Friends & Colleagues,

On behalf of my distinguished colleague Professor Jia Hu and Congress Secretaries Professors You-Sheng Mao, Wen-Gang Wei and Jian Aragaky, I am delighted to welcome you to the upcoming 2019 OESO biennial meeting in historic Beijing. This will be the 15th OESO World Conference, but the first OESO World Conference to be held in Asia and only the second to be held outside of Europe.

OESO is a unique organization focused on multidisciplinary study of the esophagus in a format that allows true multi-disciplinary conversation and collaboration in a manner unmatched by traditional society meetings. The ability to have discussion with gastroenterologists, surgeons, otolaryngologists, pathologists, allergists, oncologists, radiologists, basic scientists and other specialties with regards to specific esophageal issues is what makes OESO such a rewarding venue and brings us back time after time.

The core program will focus on short directed questions to key faculty to spark discussion and debate, while the corollary program will allow discussion of novel technology, a review of key updates in various disciplines related to the esophagus, and discussion of key controversies in our field. The meeting will be designed to maximize contact between attendees in a stimulating, fun environment in the hopes of furthering discussions to shape the future of our field.

We are also privileged to be sharing this world congress with the National Cancer Center of China, the Cancer Foundation of China, the Committee of Esophageal Cancer, CACA, the Committee of Endoscopy, CACA, the Committee of Cancer Epidemiology, CACA, the Committee of Cancer Etiology, CACA, and the Chinese Society for diseases of the esophagus – making this World Congress the largest to date.

In addition to the compelling academics, we hope to engage you in what we promise to be a wonderful social program. While details of this are still being finalized, we are hoping that all the attendees will have time to socialize while taking in the wonderful cooking, culture and sights of historic and beautiful Beijing.

We hope to see you in November 2019!

John D. Clarke
Co-President of the Congress

15th OESO World Conference for Esophageal Diseases
第十五届世界食管疾病大会

Letter of Invitation

Dear Professor/ Specialist,

It is my honor to invite you to attend the 15th OESO World Conference for Esophageal Diseases, which will be held from Nov. 7th to Nov. 10th, 2019 at China National Convention Center, Beijing, China.

The 15th OESO World Conference for Esophageal Diseases will be organized by OESO, China National Cancer Center, and Cancer Foundation of China, which will gather specialists working in the field of esophageal diseases from around the world and focuses on the new technology, multidisciplinary treatment principles, cooperation and innovations in future on the esophageal cancer and benign diseases.

For your outstanding academic achievements and influence, we sincerely invite you to attend this conference and to share your precious experience! We are looking forward to welcoming you in Beijing!

Conference Chairman: Prof. Jie He
Academician of Chinese Academy of Sciences
Director of National Cancer Center of China

PROGRAM AGENDA November 9, 2019

The 15th OESO World Conference for Esophageal Diseases
OESO Plenary Meeting: Cancer Epidemiology & Cance Etiology and Basic Research

November 9, 2019 08:00 - 11:30 (1F multi-function hall A+B)

08:00 - 09:30 Chairman: Youlin Qiao, Christian Abnet

08:00-08:30	The burden of Esophageal cancer: a global perspective Les Mery (International Agency for Research on Cancer)	
08:30-09:00	Microbiome researches on GI cancer. Christian Abnet (National Cancer Institute)	
09:00-09:30	Big data approaches to advance esophageal cancer prevention Yawei Zhang (Yale Cancer Center)	
09:30-10:00	Tea Break	

10:00 - 10:30 Chairman: Zhihua Liu

10:00-10:30	How tumor recruits cancer - associated fibroblasts to establish a suitable microenvironment in esophageal squamous cell carcinoma?	Xinyuan Guan
10:30-11:00	Molecular basis of esophageal squamous cell carcinoma —— On the issues in cancer molecular biology research	Mingrong Wang
11:00-11:30	Tumor of the microenvironment of esophageal cancer	Hana Ratnawati

The 15th OESO World Conference for Esophageal Diseases
OESO Benign Disease of Esophagus

November 9, 2019 07:55 - 11:50 (3F 308)

07:55-08:00	Introduction	Longqi Chen

08:00 - 10:10 Chairman: Peng Zhang, Lei Yu

08:00-08:20	Correlation between esophagitis grades and reflux	Xiaohua Hou

26/P

Presented in **The 15th OESO WORLD CONFERENCE FOR ESOPHAGEAL DISEASES - Beijing, 8-10 November 2020** as **Invited Speaker.**

THE ROLE OF TUMOR MICROENVIRONMENT IN THE PATHOGENESIS OF ESOPHAGEAL CANCER

Hana Ratnawati

Faculty of Medicine, Maranatha Christian University, Bandung – Indonesia

Abstract

Esophageal cancer ranks sixth as the deadliest cancers worldwide and the incidence is rapidly increasing over the past few decades. Risk factors play a big role in the pathogenesis of esophageal cancer and gastroesophageal reflux and inflammation are the main risk factors which can lead to Barrett's esophagus and metaplasia of the esophagus epithel. Chronic inflammation will affect the surrounding immune cells and trigger transdifferentiation and transcommitment of the esophageal epithel and support the pathogenesis of esophageal cancer. The chronic inflammatory process in Barrett's esophagus will cause ischemia, edema and activate the immune cells in the tumor microenvironment and induces activation of inflammatory signaling pathways through IL-6/STAT3/NFκB and leads to activation of gene transcription and COX-2 enzym activity that promote cell proliferation and survival. This pathway hijacked by the cancer cell to promote growth, survival, angiogenesis and metastasis. Chronic inflammation is clearly involved in the formation of the tumor microenvironment and development of cancer. A researcher said that human tumors as `wounds that do not heal'.

Introduction

According to WHO data in 2012, esophageal cancer ranks the 8th most common cancer and it ranks sixth as the deadliest cancers worldwide and the incidence is rapidly increasing over the past few decades[1,2]. The incidence increases with age, and the peaks is in the 6th and 7th decades with a male to female ratio of about 3 : 1 and in adenocarcinoma men was on average four times greater than in women[3,4]. There are two major histological types of esophageal cancer, the adenocarcinoma and squamous cell carcinoma. The highest burden of squamous cell carcinoma was found in South-Eastern and Central Asia and the most common of adenocarcinoma was found in Northern and Western Europe, Northern America and Oceania. Adenocarcinoma typically develop in the lower third of the esophagus and the esophagogastric junction *a*nd originate predominantly from Barrett mucosa, squamous cell carcinoma occurs mostly in the upper two-thirds of the oesophagus[5,6].

Risk factors play a big role in the pathogenesis of esophageal cancer. Esophageal squamous cell carcinoma is common in the elderly and people with dark skin with the main risk factors are smoking, alcohol and nitrosamines in preserved foods. Meanwhile, the main risk factor for esophageal adenocarcinoma is gastroesophageal reflux disease (GERD), which is the increase of stomach acid into the esophagus and irritates the surface of the esophagus. Repeated occurrences of GERD result in the esophageal epithelial cells to Barrett's esophagus, which later will develop into esophageal cancer. Obesity is also a risk factor for adenocarcinoma, this is due to the higher risk of GERD in those who are overweight[1,7].

Barrets esophagus as risk factor of esophageal adenocarcinoma.

The esophagus is a fibromuscular tube that connects the pharynx to the stomach and consists of four layers namely mucosa, submucosa, muscularis and adventitia. A thick stratified squamous non-keratinized epithelium lines the esophagus and is supported by a connective tissue of the lamina propria where lymphoid nodules and scattered leukocytes can be found[8]. if someone experiences acid stomach reflux for a long time, which known as GERD, it will affect the characteristic of the epithelium in the esophagus.

Chronic esophageal injury caused by GERD will be accompanied by inflammation and converting the squamous mucosa in the esophagus into columnar mucosa. This change will trigger metaplasia, which is the conversion of one type of tissue to another. Wang (2017), uses the terms transdifferentiation and transcommitment for the pathogenesis of Barrett's esophagus where squamous cells in the esophageal mucosa turn into columnar cells directly through molecular reprogramming without cell division called transdifferentiation, or indirectly through squamous epithelial stem cells and cell division known as transcommitment[9,10].

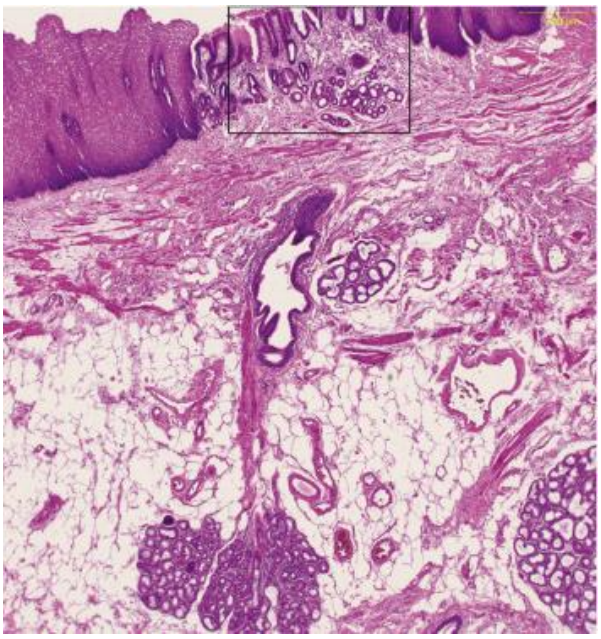

Fig 1. Barrett's esophagus shows the presence of columnar epithelium in squamous mucosa, an esophageal mucosal glands and duct is present beneath the columnar island (H&E, 10×)[10].

Study from Agoston *et al* there is a similarity between the wound healing response and development of a columnar-lined esophagus in rats after esophagojejunostomy. It can be said that this metaplasia is an initial wound healing response to chronic inflammation due to stomach acid[10,11].

The change from stratified squamous cells in the normal esophagus to columnar cells after chronic inflammation begins with the cells in the jejunum migrating to the mesenchyme under the lining of the esophageal ulcer. This means that there is a cell transition, known as epithelial-mesenchymal transition, a process in which epithelial cells tethered to one another by adhesion molecules such as E-cadherin become a mesenchymal-like cells with the ability to migrate, this is a wound healing process[11,12].

Tumor Microenvironment affects the Cancer Growth.

In year 2000, Hanahan and Weinberg proposed six hallmarks of cancer that provides a framework for understanding the remarkable diversity of neoplastic diseases. The hallmarks of cancer yang proposed by Hanahan, consists of self-sufficiency in growth signals, evading apoptosis, insensitivity to anti-growth signals, sustained angiogenesis, tissue invation and metastasis and limitless replicative potential. The six hallmarks are more focused on cancer cell. focus only the Cancer cell[13].

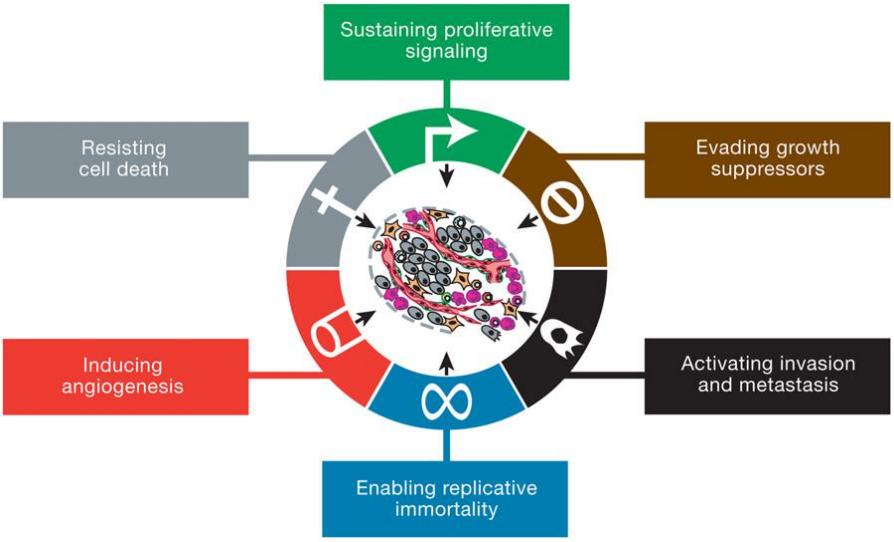

Fig. 2 The six hallmarks of cancer[15]

Besides the factors that are directly related to tumor cells, it turns out that there are interactions between tumor cells and components of the tumor stroma, known as the tumor microenvironment (TME). Each cancer cell is exposed to a complex mixture of signals from its microenvironment. This TME has a major impact on tumor development and contributes to most of the features of tumor cells, even converting the cells around the tumor into cells that are beneficial for cancer development.

The TME is created by the tumor and dominated by the cells which is induced by the tumor cells[14]. That's why a decade later, in 2011, Hanahan and Weinberg address two new emerging hallmark which broaden the scope of the conceptualization from six hallmarks of cancer with two characteristics crucial to cancer phenotypes, which are the constitution and signaling interactions of the TME[15].

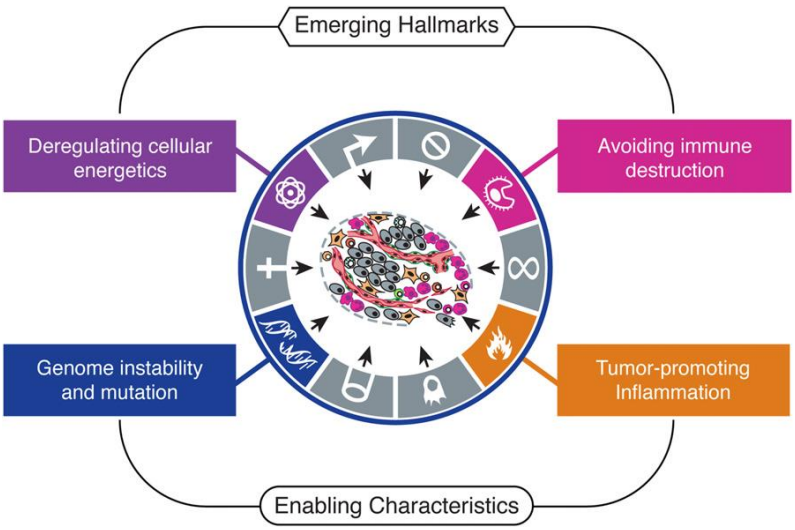

Fig. 3 The emerging halmarks of cancer[15]

The characteristics of this new cancer are involved in pathogenesis of almost all cancers. The first is the ability to modify, or reprogram, cell metabolism to effectively support cancer cell proliferation. The second is, cancer cells can avoid attack by cells in the immune system, particularly by T and B lymphocytes, macrophages, and NK cells. In addition, two other characteristics are genomic instability and genetic alterations that drive tumor progression. The innate immune cells as well as adaptive immune cells in the TME contribute to the tumor growth and progression, even tumor metastasis[15,16]. Innate immune cells in the TME, which are designed to fight infection and wounds healing through inflammation, can instead lead to support for cancer cell growth, known as tumor-promoting consequences of inflammatory responses. The role of inflammation in tumor cells actually has occurred since the beginning, the initiation, promotion and progression phases[15].

The role of TME in the Pathogenesis of Esophageal Cancer

The histological types of esophageal cancer mostly are squamous cell carcinoma and adenocarcinoma with the major risk factors are smoking and alcohol consumption. In squamous cell carcinoma, alcohol is the primary risk factor but when combination with smoking will increase the risk. Alcohol can damage the DNA and alcohol as a fat-soluble compound will make the carcinogen from the tobacco penetrate the esophageal easier. Then followed by inflammatory process, leads to dysplasia and malignancy[7].

In adenocarcinoma esophagus, gastroesophageal reflux is the main risk factor, which can lead to Barrett's esophagus and metaplasia of the esophagus epithel. Another risk factor of the adenocarcinoma esophagus is obesity, due to the adipocytes can create an inflammation and promote tumor development through the release of adipokines and cytokines. The adipocytes in the TME also will supply energy and support tumor-growth and progression[17].

From the above statement it can be said that chronic inflammation which influence the immune cells in the TME plays an important role in the pathogenesis of esophageal cancer. Chronic esophageal inflammation will trigger transdifferentiation and transcommitment of the esophageal epithel and this support the pathogenesis of Barrett's esophagus and at the end support the pathogenesis of esophageal cancer[9,10]. The chronic inflammatory process will cause ischemia, edema and changes in the TME among others activate the immune cells and finally increase the angiogenesis. Chronic inflammation is clearly involved in the formation of the tumor microenvironment and is referred to as the host reaction to tumors, although it may be more as a tumor-promoting

reaction. Dworak coined the phrase describing human tumors as `wounds that do not heal'[14].

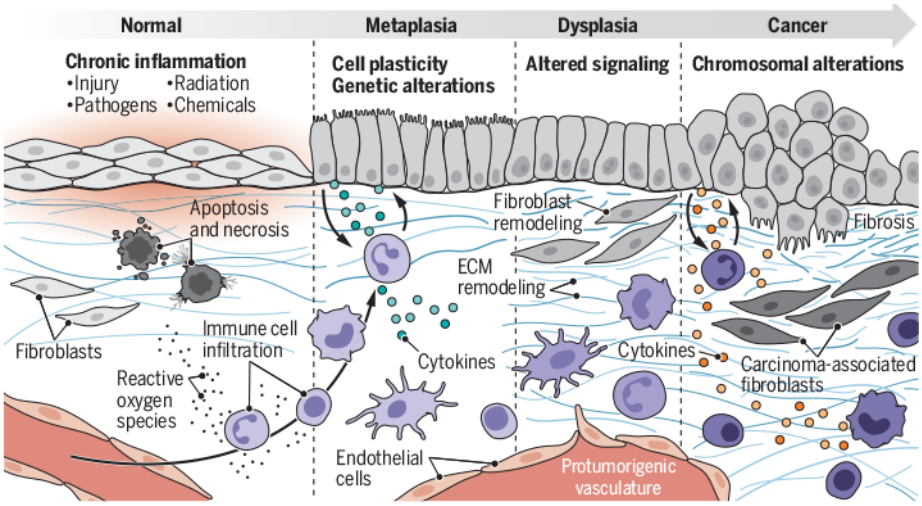

Fig. 4 Chronic inflammation-associated cancer pathogenesis

In figure 4 showed that inflammation is a critical component of tumor progression. Cancers can arise from sites of infection, chronic irritation and inflammation. In response to tissue injury, signals start and maintain a host response to "heal" the damage. This involves getting "activated" leukocytes to the proper damaged location. Adhesion molecules and integrins with their respective receptors/ligands modulate leucocytes rapid adhesion, activation of gene expression, and transmigration into the tissue. Expression of chemokines attract specific leucocytes populations and promote the natural progression of the inflammatory response. The "normal" inflammatory response associated with wound healing is self-limiting. Dysregulation of key steps leads to abnormalities and pathogenesis neoplasia. Once the wound is healed, the reciprocal signaling subsides.

In the pathogenesis of esophageal cancer, the chronic inflammation induces activation of inflammatory signaling pathways and leads to activation of gene transcription and enzym activity that promote cell proliferation and survival.

The primary pathways implicated in esophageal cancer are:

a. Interleukin-6/STAT3 pathway

IL-6 is a cytokine that signals activation of several molecules and also transcription factor STAT1 and STAT3. In normal cell, IL-6/STAT3 pathway allows normal cells to survive, but in carcinogenesis the pathway is hijacked by the cancer cell to promote growth, survival, angiogenesis and metastasis, even suppress apoptosis and inhibit anti-tumor immunity[18]. IL-6 has been shown to drive expansion of pro-tumorigenic myeloid-

derived suppressor, while STAT3 activation leads to production of anti-apoptotic molecules like myeloid cell differentiation protein-1[19].

b. Nuclear factor-kappaB (NF-κB)

NF-κB is a transcription factors that regulate survival, proliferation, and cytokine production in normal cell. In normal conditions, NF-κB is maintained in an inactive state, but in inflammation condition, NF-κB become active and will activate genes involved in carcinogenesis and immune evasion. NF-κB expressed highly in esophageal adenocarcinoma and esophageal squamous cell cancer. Activation of this mechanism is thought to be a key link between an inflammatory microenvironment and cancer development[19].

In fact, NF-κB/IL-6/STAT3 share several downstream effectors, that enhances the resilience of cancer cells even if one of these pathways is inhibited. thought to form a self-sustaining positive feedback loop for signal amplification.

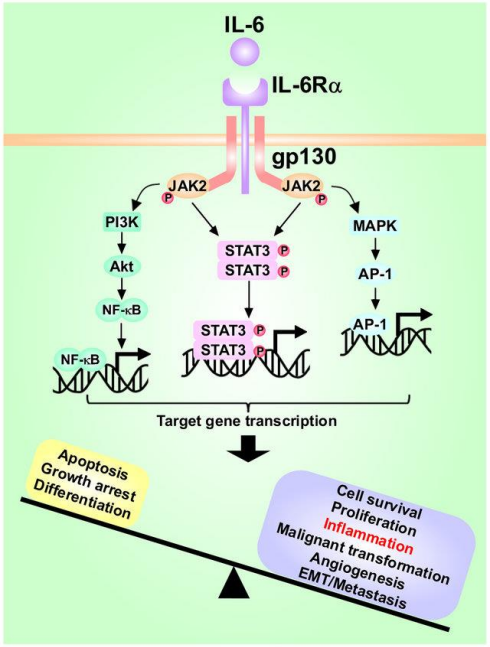

Fig. 5 The role of IL-6/STAT3/NFκB signaling pathway in carcinogenesis[20]

The signaling pathway of IL-6/STAT3/NFκB in carcinogenesis showed in Fig 5, firstly IL-6 binds to the receptor and activating downstream signaling pathways through JAK/STAT3, PI3K/Akt and MAPK pathways, which activate NFκB and will promote proliferation, cell survival, inflammatory amplification, malignant transformation, angiogenesis and metastasis[20].

c. Cyclooxygenase-2 (COX-2)

COX-2 is an inflammatory enzyme which responsible for the production of prostaglandin E2. This COX-2 expression is elevated in Barrett's esophagus and esophageal adenocarcinoma and in esophageal squamous cell carcinoma there is a correlation between COX-2 expression and the degree of dysplasia. Several studies showed that COX-2 inhibitor can suppress inflammation and cell growth and lead to decreased cell proliferation[19].

CONCLUSION

- Esophageal cancer ranks the 8th most common cancer and it ranks sixth as the deadliest cancers worldwide and the incidence is rapidly increasing over the past few decades.
- Chronic esophageal injury caused by GERD will be accompanied by inflammation via transdifferentiation and transcommitment as the pathogenesis of Barrett's esophagus.
- Chronic inflammation and tumor microenvironment play an important role in pathogenesis of esophageal cancer through the IL-6/STAT3/NFκB signaling pathway and COX-2 inflammation enzym.

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