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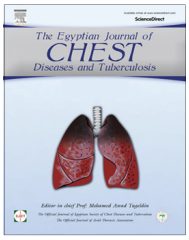

ORIGINAL ARTICLE

Is toll like receptor 4 a common pathway hypothesis for development of lung cancer and idiopathic pulmonary fibrosis?

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KEYWORDS

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Abstract Idiopathic pulmonary fibrosis (IPF) is a specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause, occurring primarily in older adults and limited to the lungs. IPF is a disease with similarities and links to cancer biology whose main event is aberrant cell proliferation. Although toll like receptors (TLRs) are essential for protective immunity, inappropriate TLR responses contribute to inflammation. Chronic inflammation is one of the risk factors and features of cancer. It can affect any stage of tumorigenesis and migration of cancer cell.

Aim of work: To investigate the key role of TLR4 expression in the development and progression of lung cancer and IPF and its contribution as a common pathway in the development of both.

Methods: This study included 16 IPF patients, 20 lung cancer patients and 23 control subjects. All patients were subjected to full history taking, detailed clinical examination, radiological assessment, bronchoscopic biopsies and serum samples for measurement of TLR4 expression. TLR4 was measured in serum of all control subjects and in bronchoscopic biopsies for only five of them.

Results: TLR4 expression was higher in serum and tissue biopsies of IPF and lung cancer patients than that in the control group; however the highest level of LTR4 expression in serum was observed in the IPF group and the highest level in tissue biopsy was observed in the lung cancer group. TLR4 levels were not significantly different between the three studied groups. There was a significant association between TLR4 expression in tissue biopsy and distant metastasis among NSCLC cases ($p = 0.006$).

Conclusion: Our results support that TLR4 pathway may be a common contribution to both diseases. There was association between distant metastasis and TLR4 expression. Further studies are needed to evaluate the TLR4 prognostic value for tumor progression and its expression in precancerous lesions.

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Introduction

Idiopathic pulmonary fibrosis is a specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause, occurring primarily in older adults and limited to the lungs [1]. IPF is a disease with similarities and links to cancer biology. A number of pathogenetic hypotheses are shared by both fatal diseases, whose main event is aberrant cell proliferation [2]. Human TLRs are a family of trans-membrane receptors that consist of ten members and play a key role in innate immune defense, particularly in inflammatory response against various invading exogenous pathogens [3,4].

Although TLRs are essential for protective immunity against infection, inappropriate TLR responses contribute to acute and chronic inflammation, as well as to systemic autoimmune diseases [5,6]. Activation of TLR signaling in the steady state maintains tissue architecture. However, in the presence of deregulated inflammation and/or tissue injury, as occurs in fibrogenesis and tumorigenesis, the TLR-driven tissue response may promote tissue remodeling, neoangiogenesis and tumor growth by mechanisms that are still poorly defined [7].

TLRs are expressed in a variety of cells, including type II alveolar epithelial cells, airway epithelial, smooth muscle cells, and fibroblasts [8]. TLR4 is a key regulator of the pro-inflammatory transcription factor nuclear factor kappa B (NF-κB) and plays a dominant role in mediating sterile tissue damage. IκB kinase (IKK) activation leads to the dissociation of NF-κB from IκB and its subsequent activation [9].

The mechanism of TLR4 activation involves several auxiliary proteins as well as a co-receptor ''myeloid differentiation factor 2'' (MD-2) [10]. MD-2 is a soluble protein that represents the binding site for the acyl chains of lipid A. Lipid A is usually composed of 6 acyl chains, but only 5 of them bind to MD-2. The 6th acyl chain interacts with residues on TLR4. This MD-2/TLR4 heterodimerization is a prerequisite for the activation of the TLR4 signaling cascade [11,12]. The endotoxin/MD-2/TLR4 heterodimer can trigger the transcription of both proinflammatory cytokines as well as type I interferons [10].

It is therefore not too surprising that TLR4 activation affects not only the immune response against invading Gram-negative bacteria but is also involved in chronic inflammation, autoimmune diseases and malignancies. TLR4 signaling in cancer is considered a double-edged sword. If TLR4 is activated on immune cells, it can enhance anti-tumor immunity. On the other hand, chronic inflammation is a major risk factor in cancer development [13].

Chronic inflammation has emerged as one of the main risk factors and features of cancer. It can affect any stage of tumorigenesis, generating a microenvironment conducive to tumor development and progression, and promoting the survival, proliferation and migration of cancer cells. Thus, many cancers can arise from local irritation, inflammation and chronic infection. Changes in proteins or receptors involved in the inflammatory and immune responses may contribute to an increased risk of developing cancer. TLRs activate the NF-κB pathway, the main regulatory inflammation signaling pathway, and this activation is involved in the pathogenesis of cancer [14].

Emerging evidence suggests that chemoresistance is promoted by substances released from dead and damaged cells that activate the host repair program orchestrated by TLR4. TLR4 is often over-expressed in malignant and tumor infiltrating immune cells. TLR4 activation promotes local and systemic inflammation, leading to the induction of multiple circuits that create a regenerative environment favoring local recurrence and metastasis. Of particular importance is TLR4-mediated recruitment of endothelial progenitors derived from immature myeloid cells. These cells play a major role in rebuilding tumor-associated lymphatic and blood vessels, thereby promoting lymphatic and hematogenous metastasis [15].

The aim of the present study was to investigate the key role of TLR4 expression in the development and progression of lung cancer and IPF and to study TLR4 contribution as a common pathway in the development of both.

Patients and methods

The present study included 59 subjects who were sub-grouped into; sixteen patients with the diagnosis of IPF, twenty patients with bronchogenic carcinoma and twenty-three control subjects. All patients were recruited from chest departments, Cairo University and Fayoum University Hospitals in the period from January 2014 to June 2015. Informed consent was obtained from all patients who participated in the study. The study was approved by the research ethics committee, Faculty of Medicine, Cairo and Fayoum Universities.

IPF: They were diagnosed based on the guidelines of the international consensus statement produced as a collaborative effort from the ATS, ERS, JRS and ALAT [1]. All IPF patients were newly diagnosed and had not received any treatment and patients with any known cause of pulmonary fibrosis, such as a systemic connective tissue disorder, were excluded by both immunologic screening and rheumatological clinical evaluation. All IPF patients were subjected to full history taking including smoking and occupational history, detailed clinical examination, arterial blood gases analysis, spirometry, 6-min walk test, echocardiography with assessment of the pulmonary artery systolic pressure and high-resolution computed tomography of the chest. For evaluation of interstitial involvement with HRCT, fibrosis score or interstitial score as described by Gay et al. in (1998) [16] was used. In this method each lobe of the lung was separately scored for the presence, distribution and extent of honeycombing and interlobular septal thickening on a scale of 0–5 as follows: (0) no interstitial disease, (1) septal thickening without honeycombing, (2) honeycombing involving up to 25% of the lobe, (3) honeycombing involving 25–49% of the lobe, (4) honeycombing involving 50–75% of the lobe, (5) honeycombing involving $>75\%$ of the lobe. Honeycomb cysts were defined as localized areas of decreased attenuation with well defined walls. The lingula was scored as a separate lobe. After each lobe was scored individually, an average score for all lobes was obtained and used for the statistical analysis.

Bronchogenic carcinoma: All patients were subjected to full history taking including smoking history. Patients underwent radiological assessment to detect primary tumor site, pleural or mediastinal lymph nodes involvement and distant metastasis. The patients included in the study were diagnosed based on histopathological criteria from endobronchial biopsies and they had not received any treatment for lung cancer. The