Role of cytokines in chronic pancreatitis

Abstract: Expression of pro-inflammatory and regulatory cytokines plays a key role in the pathogenesis of acute and chronic pancreatitis and is involved in the development of pancreatic necrosis and pancreatic fibrosis. Cytokines entering the bloodstream in the context of the local inflammatory reactions cause a systemic toxic syndrome with multiple organ failures, that are frequently resulting in mortality in acute pancreatitis. The scientific evidence clearly suggests that in acute pancreatitis a predominance of pro-inflammatory cytokines are prevalent anti-inflammatory cytokines potentiate the inflammatory process and the increase of regulatory cytokines, including their exogenous administration, reduces the severity of the inflammatory reaction, or leads to its relief. This review summarizes our current understanding of the role cytokines play in pancreatic cancer’s resilience and its resistance to treatment focusing on two major pro-inflammatory cytokines, its role in tumor microenvironment necessary for growth and metastasis, and their potential for therapeutic and diagnostic procedures.

Keywords: Chronic pancreatitis, Pancreatic carcinoma, cytokines.

Introduction. The pathogenic role of cytokines in the development of pancreatic diseases is of major scientific and clinical interest for clinical practice, a marker for the severity and prognosis of acute pancreatitis (AP) attacks or chronic pancreatitis (CP) would be of great interest. At the same time, given the lack of a clear understanding of the pathophysiology of AP, apart from the diagnostic relevance of pancreatic enzymes and other pancreatic proteins (e.g., pancreatitis-associated protein, PAT), the chemokine and cytokine levels may be useful for the diagnosis and assessment of a current episode of AP or CP.

In recent years, pro-inflammatory and regulatory cytokines play an increasing role in the pathogenesis of AP and CP and are in-
involved in the development of pancreatic necrosis and fibrosis. Pancreatic cancer is the most lethal gastrointestinal (GI) cancers, with a 5-year survival rate of only a 3–5%. This cancer is characterized by a high mortality rate, rapid progression, and resistance to chemo and radiation therapy. While surgical resection is the only curative treatment for pancreatic cancer, only less than 15% patients are eligible for surgery. Many studies have demonstrated the wide-spread involvement of cytokines in all stages of cancer development. The question remains, however, whether such a functionally pleiotropic and chemically diverse class of molecules can be targeted towards the treatment of pancreatic cancer. This review summarizes the current understanding of the role two major pro-inflammatory cytokines in pancreatic cancer and its resistance to treatment focusing on two major pro-inflammatory cytokines, especially their role in tumor microenvironment necessary for growth and metastasis, and their potential therapeutic and diagnostic use. Cytokines are a vast and diverse group of glycosylated peptides produced by virtually all nucleated cells in the human body. They play important roles in regulating cell growth, inflammation, and tumor metastasis. One of the characteristic features of pancreatic cancer is its rapid growth and aggressive metastasising which the overexpression of pro-inflammatory cytokines such as interleukin-6 (IL-6) and interleukin-8 (IL-8) is implicated [3]. These pro-inflammatory cytokines play a critical role in the activation of signal pathways controlling cell growth and angiogenesis, e.g., through the vascular endothelial growth factor (VEGF), a cytokine which enhances angiogenesis and facilitates metastasis [2]. Targeting these pro-inflammatory cytokines may represent a novel molecular therapeutic strategy. IL-6 has been shown to be overexpressed in human pancreas cancer cells, and exogenous IL-6 increased the secretion of multiple Th2 type cytokines. IL-6 also activated extracellular signal-regulated kinase 2 (ERK2) signaling pathways in pancreas cancer cells, indicating that IL-6 may be involved in promoting human pancreas cancer development through a Th2 type cytokine environment which up-regulates cell proliferation and angiogenesis [4]. Recent studies demonstrated that IL-8 was up-regulated under hypoxic condition mimicking the human disease. IL-8 up-regulated the expression of VEGF and activated ERK1/2 signaling pathways in pancreas cancer cells. These data suggest that IL-8 might be a key player in human pancreas cancer and that targeting IL-8 together with other angiogenesis pathways could be an effective treatment for pancreas cancer [5]. The two cytokines IL-6 and IL-8, therefore, are of major interest of current oncogenic cytokine research because they play a key role in pancreas cancer.

The aim of the study presented was to define the role of the immune system and of cytokines in the diagnosis and treatment of chronic pancreatitis and pancreas cancer.

**Materials and methods.** The research was conducted in the Clinic of Internal Medicine II, University Hospital of Freiburg, Germany.

The study included a prospective cohort 47 patients with chronic pancreatitis. Follow-up was on average 6 months. The mean age of patients with CP in the acute phase was 51.7 ± 2.9 years. Diagnosis was made on the basis of clinical, laboratory and imaging analyses, including past history, complaints, physical examination, and laboratory analyses of blood and urine ultrasonography (US) and computed tomography (CT) of the abdomen. Concentration of pancreatic elastase-1 in the stool of patients was determined by enzyme immunoassay (ELISA). The level of cytokines IL-1β, IL-6, IL-8, IL-10, TNF-α, TGF-β was determined using commercial test systems.

**Results and discussion.** During an exacerbation of CP, the expression level of all analysed cytokines was significantly higher than that of healthy controls. The expression of pro-inflammatory cytokines IL-1β, IL-8 and TNF-α was 10.3-, 10.2-and 8.2-fold higher, respectively, while the levels of the pro-inflammatory cytokines IL-1β and IL-10 was 7.5-and 5.6–times higher, respectively (Table 1). All we divided patients into three groups depending on the level of elastase in the stool. Group 1 patients with elastase levels above 100, the second group of patients with a level of 100 elastase in third group 100 below. (The rate of elastase in the stool of healthy human 200mg/kg/g).

**Table 1. – Cytokine levels in serum of different groups of patients with acute exacerbation of chronic pancreatitis**

<table>
<thead>
<tr>
<th>Cytokines</th>
<th>Levels (pg/ml)</th>
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<tbody>
<tr>
<td></td>
<td>Control</td>
</tr>
<tr>
<td>IL-1β</td>
<td>22.7 ± 1.9</td>
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<tr>
<td>IL-6</td>
<td>28.5 ± 1.1</td>
</tr>
<tr>
<td>IL-8</td>
<td>19.1 ± 1.1</td>
</tr>
<tr>
<td>IL-10</td>
<td>18.6 ± 0.8</td>
</tr>
<tr>
<td>TNF-α</td>
<td>43.5 ± 6.1</td>
</tr>
<tr>
<td>TGF-β</td>
<td>37.9 ± 2.2</td>
</tr>
</tbody>
</table>

*p<0.001 relative to control

Mean values of TGF-β were significantly higher than control values. This increase of 5.3-fold compared to controls was however less. The highest expression was found for IL-1β and IL-8 which may further potentiate the cascade of inflammatory reactions. There was a direct correlation between the severity of abdominal pain and the levels of pro-inflammatory cytokines IL-1β, IL-8 and TNF-α. The levels of IL-1, IL-6, IL-8, IL-10 and TNF-α correlated with the elevations of ALT and AST while TGF-β correlated with activities of pancreatic amylase, lipase. Expression of IL-8 was highest in group 1 and decreased with worsening of exocrine insufficiency. A direct correlation between the level of fecal elastase and serum concentration of IL-8 in the period of exacerbation of CP. With respect to TNF-α levels similar changes were detected. Compared to healthy individuals the levels of TNF-α were 8.8-, 8.2-and 7.4-fold, respectively, higher. A direct correlation was found between the level of stool elastase and the serum concentration of IL-8 during exacerbation of CP. The level of IL-10 was significantly higher in all the groups, 6.0-, 5.5-and 5.0-fold, respectively, as compared to controls. Average values of TGF-β in the different groups were significantly higher than in control with a 3.2-, 5.4-and 8.4-fold increase, respectively. The maximum values were found in group 3 with a significantly elevated level of expression of TGF-β in the 1st and 2nd groups. There was a direct correlation between the level of stool elastase and the expression of TGF-β during exacerbation of CP.

Chronic inflammatory processes have become the center of research in cancer pathogenesis, treatment and prevention. It is now...
well-known that cytokines play a role in inflammation as well as in malignant transformation and the promotion of cancer progression and metastasis [6]. IL-8 is strongly associated with chronic pancreatitis which increases the risk of pancreas cancer by a factor of 20 or more due to the convergence of inflammatory mediators and cytokines into a common pathway [7]. Thus, IL-8 is activated by inflammation, which in turn acts through a positive paracrine feedback loop via up-regulation of several inflammatory mediators to locally maintain inflammation and promote angiogenesis [8]. Further, IL-6 also enhances the secretion of pro-inflammatory cytokines typically expressed in Th2 lymphocytes and plays a similarly important role in inflammation [4]. The current molecular therapeutic aims are targeted at the inhibition of these common pathways and thereby the malignant transformation of pancreas cells the communication between the tumor cells and the stromal fibroblasts as well as the immune effectors is very complicated, however. For instance, IL-8 binds to multiple receptors, and is induced, apart from hypoxia, by several factors such as NO, oxidative stress, and acidosis. At the same time both IL-8 and IL-6 are induced TNF-α [2]. Therefore, the detailed understanding of the entirety of the wide spectrum of chemical cross-talk involved in establishing the tumor microenvironment is key for future therapeutic strategies. Thus, with the more fundamental understanding of the pathogenesis of pancreas cancer, novel diagnostic, therapeutic and preventive targets will be identified improving the prognosis of patients with pancreas diseases.

Conclusions and perspectives. The analysis of patients with chronic pancreatitis showed that even during remission there are significant alterations of the the cytokine network and the balance between pro- and anti-inflammatory components. The data obtained open the possibility of predicting natural course of CP, including disease recurrence and progress based on cytokine levels and their imbalance. The level of pro-inflammatory and anti-inflammatory cytokines can predict clinical deterioration and the probability of relapse. The he study demonstrates that in patients with CP cytokines are more sensitive laboratory markers than the traditional parameters. Thus, as we begin to develop a more fundamental understanding of the mechanisms underlying the aggressive natural course of pancreas cancer, novel diagnostic, therapeutic and preventive targets will be identified that will result in an improved prognosis of patients with diseases of the pancreas.

References:


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Life style of the patients suffering with bronchial asthma

Abstract: This article studied on the questionnaire lifestyle, medical activity in patients with bronchial asthma, the factors leading to the disease of 670 persons infected with asthma and 420 persons not infected with this disease, but living in the similar conditions.

Keywords: bronchial asthma, quality of life, mode of life, medical active.

Bronchial asthma is disease of respiratory ways, including the pathological process flowing with chronic persistor inflammation and obstruction of bronchial tubes that it is possible to observe at attack suffocation or asthmatic condition [1; 3; 6; 13; 14; 15].

Despite improvement of diagnostics and methods of treatment of the disease, on a global scale suffering a bronchial asthma, and also cases of physical inability and death rate as a result of this disease increases. Basically, the cases having risk in a life of patients — long heavy attacks of suffocation which are resistant active broncholytic therapies, strongly expressed respiratory insufficiency because of what the present disease is vital topic of modern medicine [2; 5; 8; 11] amplify.

On threshold XXI in all potential researches 3 global problems get to eyes concerning bronchial asthma. First is disease very widespread and such tendency will proceed further the next decade, secondly — problem of bronchial asthma left because of limits of