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Review article

Novel potential biomarkers for pancreatic cancer – A systematic review

Ala Litman-Zawadzka[a], Marta Łukaszewicz-Zając[b], Barbara Mroczko[a,b,*]

[a] Department of Neurodegeneration Diagnostics, Medical University of Bialystok, Bialystok, Poland
[b] Department of Biochemical Diagnostics, Medical University of Bialystok, Bialystok, Poland

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ABSTRACT

Background: It is estimated that in developed countries the incidence rate of pancreatic cancer (PC) will continue to rise and by 2020 will be the second most fatal cancer. The mortality of PC patients closely parallels the incidence rate, as this malignancy remains asymptomatic until it reaches an advanced stage of disease. Thus, novel biochemical markers that improve the management of PC patients are necessary. The aim of the work that follows is to investigate whether selected inflammatory mediators might be used in the diagnosis of PC, with the aim of improving the prognosis for PC patients.

Methods: We performed a thorough search for literature pertaining to our investigation via the MEDLINE/PubMed database.

Results: It has been proved that certain inflammatory mediators might be involved in tumor progression, such as growth, proliferation, migration and angiogenesis of tumor cells. In the present review, we summarized and referred to a number of original papers concerning the clinical significance of selected cytokines and specific inflammatory proteins such as C-reactive protein, as well as of various matrix metalloproteinases and their tissue inhibitors, as potential biomarkers for PC in comparison to well-established tumor markers for this malignancy.

Conclusion: Presented proteins might be potential biomarkers in the diagnosis and progression of PC.

1. Introduction

1.1. Pancreatic cancer

Pancreatic cancer (PC) is the fourth leading cause of cancer-related death worldwide. However, it is estimated that the incidence rate of PC in developed countries will continue to rise, making it the second most fatal cancer by 2020 [1]. PC is characterized by rapid progression, extremely poor prognosis, aggressive behavior, and limited treatment options. Generally, there are similarities between the incidence of PC and mortality rates for this malignancy [1]. Approximately 6% of patients with PC have a 5-year survival rate, which may be caused by a number of factors, especially late diagnosis [2].

The exact etiology of PC development is still not well clarified. However, there are several factors that have been suggested to increase the risk of this malignancy. These factors are in general divided into two groups: the modifiable and the non-modifiable. The first group comprises obesity, cigarette smoking and increased consumption of animal fat, whereas the non-modifiable risk factors are sex, age, inherited genetic predisposition and chronic pancreatitis (CP) [3]. Epidemiological studies conducted in the US have shown that this cancer occurs more often in African-Americans than in other racial groups [4]. In addition, it was shown that PC is more common in males than females and generally occurs in older patients, specifically adults between 60 and 80 years old [5]. Approximately 10% of all PC cases are connected with genetics. Moreover, it was observed that a family history of PC largely increases the particular risk of this malignancy progressing [6].

The largest problem in the diagnostic process of PC patients is that most cases of this malignant disease are symptomless in early stages. Unfortunately, the first clinical presentation very often occurs when the tumor has already metastasized to the lymph nodes and/or other areas of the body [7]. Common symptoms of PC are: unexplained weight loss, abdominal and back pain, bloating, nausea or vomiting, and jaundice [8]. Most tumors are generally localized in the head of the pancreas, and biliary duct obstructions are a common symptom of this malignancy. Tumors located in the body or tail of the pancreas are predominantly symptomless until the disease reaches an advanced stage of PC. The occurrence of metastases affects symptoms that occur later related to engaged organs – mostly the liver, but also the stomach and colon [3].

The diagnosis of PC is an extensive process consisting of many steps. Currently, the clinical practice is based on imaging methods, such as transabdominal ultrasonography (USG), computed tomography (CT),

* Corresponding author at: Department of Biochemical Diagnostics, Medical University of Bialystok, Waszyngtona 15 a, 15-269 Bialystok, Poland.
E-mail address: mroczko@umb.edu.pl (B. Mroczko).

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magnetic resonance imaging (MRI), MR cholangiopancreatography (MRCP), endoscopic ultrasound (EUS) and positron emission tomography (PET). However, these tests have limited usefulness because of their increased costs and use of invasive procedures [9,10]. The established tumor marker for the follow-up of PC patients is the measurement of serum concentrations of carbohydrate antigen 19-9 (CA 19-9) or carcinoembryonic antigen (CEA). However, because of low specificity and sensitivity in early stages of the disease, measuring levels of these biomarkers is not useful in the screening process. Furthermore, the serum concentrations of CA 19-9 were found to be elevated in both PC and acute and chronic pancreatitis, making the differentiation between malignant and nonmalignant diseases of the pancreas very difficult [9,10]. Although the number of novel biomarkers for diagnosis of PC has been increasing during the last couple of years, there are no biochemical markers useful in the screening of PC patients [11]. Thus, there is an urgent need to find new substances that will be helpful in the early diagnosis of patients with this cancer.

1.2. The role of inflammation in cancer development

Clinical studies have proved a strong link between CP and cancer [12]. Uncontrolled, chronic inflammation might play a role in the development of various malignancies, including PC. Thus, the synthesis of proinflammatory mediators within the tumor microenvironment contributes to tumor progression via the migration of tumor cells [13,14]. Moreover, the progression of malignant disease promotes local and systemic inflammatory responses [13]. It has been shown that cancer-associated inflammation is characterized by the infiltration of immune cells. In addition, malignant cells are also able to produce various chemokines and stimulate immune cells to constitute the inflammatory microenvironment [15]. It has been proved that selected inflammatory mediators, such as cytokines, specific inflammatory proteins such as C-reactive protein (CRP), and various matrix metalloproteinases might be involved in tumor cell growth, proliferation, migration and angiogenesis of tumor cells, including PC [16–21]. Therefore, in the present review we summarize and refer to a number of original research papers concerning the clinical significance of selected inflammatory mediators as potential biomarkers of PC in comparison to well established, classical tumor markers for PC. This review also presents the results of our previous studies, where the diagnostic and prognostic usefulness of these proteins in the sera of PC patients was assessed.

2. Materials and methods

2.1. Literature search and data extraction

We performed a comprehensive literature search using the MEDLINE/PubMed electronic database from August to September 2018 with the following search strategy (key words): “biomarker AND pancreas AND tumor”. A total of 3974 papers were found. In the next step, the search was limited to human studies written in English over the last 20 years and a total of 3541 records were found (Fig. 1). We further limited the search to articles in which the issue of PC and levels of analyzed biomarkers in PC were assessed (n = 407). Then we excluded 335 articles not containing data useful for our analysis. As a result, there remained 72 full-text articles assessed for eligibility, including: 11 publications concerned the issue of PC [1–11], 5 papers were about inflammation processes in cancer [12–16], 20 studies regarded chemokines and their specific receptors [16,22–40], 15 publications presented information about IL-6 and CRP [17,18,41–53], 10 papers dealt with hematopoietic cytokines [19,20,54–61], 9 studies involved MMPs and their tissue inhibitors [21,62–69], 2 articles were about proteomics [70,71]. In the final step, we excluded all review papers, and so 35 original publications were included in the study.

3. Results

3.1. Chemokines and their specific receptors

Chemokines are low-molecular chemotactic cytokines that regulate leukocytes’ functions, such as migration, adhesion, growth, activation and differentiation. These proteins are grouped into four classes – CC, CXC, CX3C and XC, based on the key cysteine residue positions [16]. Chemokines might also be divided into inflammatory and homeostatic as well as dual function chemokines, based on their functions. Chemokines bind to their cognate G protein-coupled receptors (GPCRs), which are seven-transmembrane domain receptors [23,24]. These molecules are able to regulate many physiological processes, such as inflammation, infection, immunological response and tissue injury reactions. In addition, clinical investigations have suggested the potential significance of various chemokines in pathological processes, including malignant diseases [25,26]. However, the potential usefulness of these proteins in the diagnosis and prognosis of PC patients still remains unclear.

It has been suggested that selected chemokines and their specific receptors might be involved in the pathogenesis of PC (Table 1) [25–27]. The CXC chemokine family is known to regulate the tumor progression, including growth, proliferation, angiogenesis and metastasis of PC cells [28]. The authors indicated the clinical usefulness of CXCL-1, CXCL-5, CXCL-8 and CXCL-12 (C-X-C motif chemokine ligand 1, 5, 8 and 12) in PC. The expression of these chemokines in PC cells was significantly higher than in benign pancreatic lesions and/or normal tissue [28–32]. In addition, CXCL-8 is a component of the tumor microenvironment; thus, this cytokine might be produced by stromal cells as well as malignant cells, including PC [28,33]. Positive CXCL-1 expression in PC cells was positively correlated with TNM stage, T classification and distant metastasis, while higher CXCL-5 expression was significantly correlated with poorer tumor differentiation, advanced stage of tumor and shorter survival of PC patients [28,31]. Moreover, PC patients with positive CXCL-1, CXCL-5 and CXCL-8 expression had significantly poorer survival compared to those with negative expression of these proteins [28–31]. In addition, elevated CXCL-1 expression in PC cells was an independent prognostic factor for the survival of PC patients [28]. The authors concluded that CXCL-1 and CXCL-8 might be sensitive markers in predicting prognosis and monitoring disease progression in PC patients [28,29]. CXCL-8 acts via the CXCR-1 receptor, which may also play a role in tumor progression, including PC. Positive expression of CXCR-1 significantly correlated with lymph node metastasis and overall decreased survival of PC patients, which suggests the CXCL-8/CXCR1 axis has an impact on the prognosis for PC patients [35]. Similar findings were indicated by Zhang et al. [32], who confirmed the role of the CXCL-12/CXCR-4 axis in the development of PC. This was confirmed by other authors as well [36]. The activation of CXCR-4 by CXCL-12 might induce the migration, invasion and angiogenesis of tumor cells [32,37,38]. However, little is known about the concentrations of selected chemokines and their specific receptors in the blood of PC patients. Serum CXCL-8 levels in PC patients were significantly higher than in patients with other digestive system tumors or with chronic and acute pancreatitis [29]. In addition, plasma CXCL-7 levels were significantly decreased in PC patients, while the combined analysis of CXCL-7 and CA19-9 may improve the discriminatory power of the former in PC [39].

The CCL-20 is a C-C motif chemokine that functions as a chemotactic cytokine via binding to the highly specific receptor CCR-6. It is suggested that CCL-20 may facilitate the migration and invasion of PC cells [40]. The authors indicated that the co-localization of CCL-20 and its specific receptor – CCR-6 promote invasion of PC, which confirms the crucial role of inflammation in the development of PC [40].

Clinical investigations have confirmed that selected chemokines, especially from the CXC family, and their specific receptors contribute to tumor growth, dissemination and local immune escape in the pathogenesis of PC.

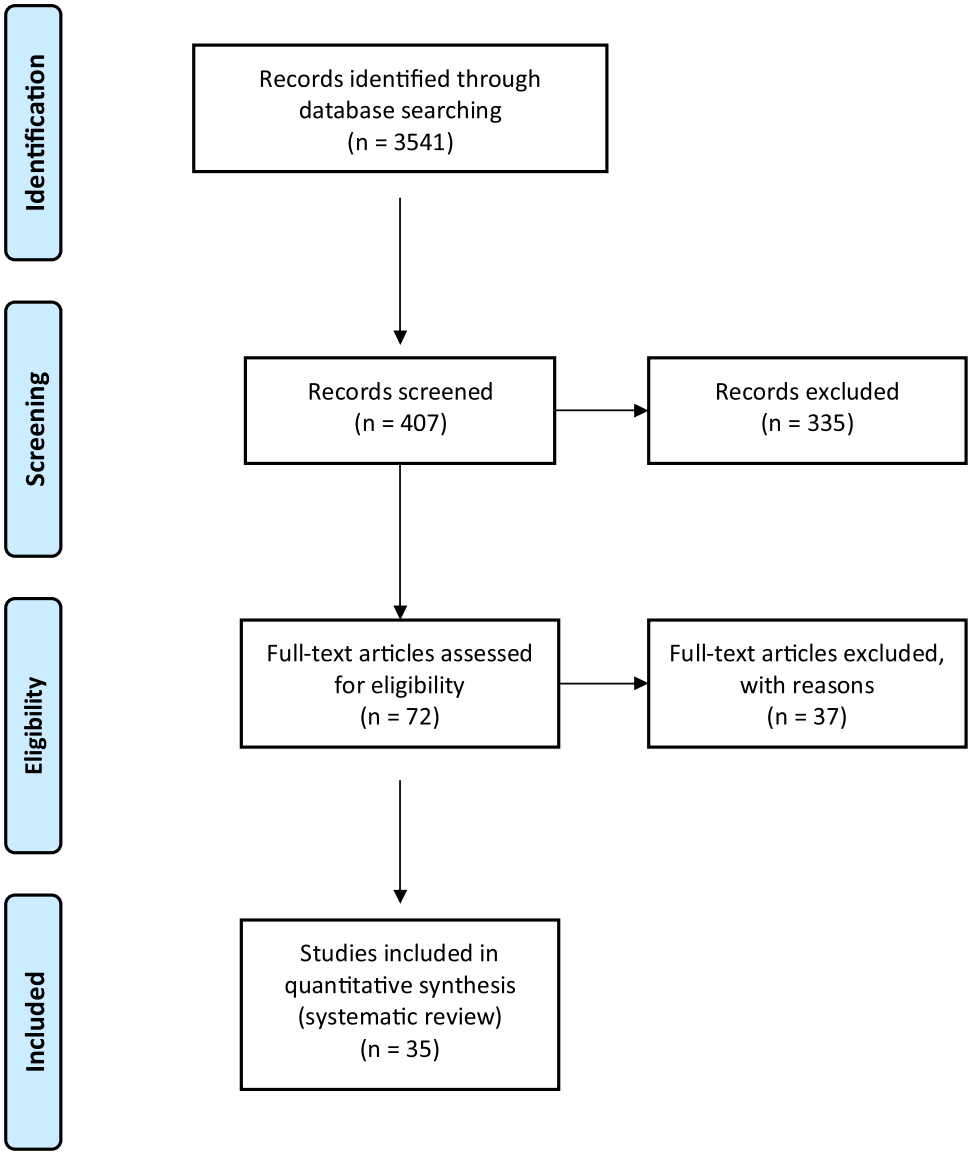

Fig. 1. PRISMA 2009 flow diagram.

Table 1
Selected chemokines and corresponding receptors involved in the development of pancreatic cancer.

Chemokines /other name	Specific receptor	References
CXCL-1 / GRO- α	CXCR-2	[28]
CXCL-5 / ENA-78	CXCR-2	[31]
CXCL-8 / IL-8	CXCR-1, CXCR-2	[29,30,33,35–39]
CXCL-12 / SDF-1	CXCR-4, CXCR-7	[32]
CXCL-7 / NAP-2	CXCR-2	[39]
CCL-20 / LARC, MIP-3a	CCR-6	[40]

3.2. Interleukin-6 and C-reactive protein

The significance of acute phase proteins has been proved in the growth and progression of many malignancies, including PC [41]. CRP is a strong acute phase protein that is produced in the hepatocytes as a response to inflammatory cytokines, such as interleukin 6 (IL-6) [17]. Some clinical investigations have indicated that tumor cells may also stimulate CRP synthesis in hepatocytes [42]. It is suggested that CRP might induce the malignant potential of neoplastic cells [43]. IL-6 is a proinflammatory cytokine that promotes the apoptosis of tumor cells by the stimulation of antitumor activity of macrophages. However, this cytokine may be also produced by the cancer cell lines and promote neoangiogenesis via stimulation of vascular endothelial growth factor (VEGF) [18,44]. Thus, IL-6 is a mediator that links inflammation and angiogenesis to malignancy [45]. Some investigators revealed higher serum levels of IL-6, interleukin 8, TNF-alfa and acute-phase proteins in the sera of patients with PC in comparison to a control group [46]. The authors indicated that concentrations of IL-6 were significantly higher in the sera of patients with PC when compared to subjects with CP [47]. In addition, it has been suggested that serum CRP and IL-6 might be used as potential negative prognostic factors for PC patients' survival [48,49]. In our previous study, the diagnostic and prognostic usefulness of these proteins in PC patients in comparison to classical tumor markers as well as the usefulness of differentiating between PC and chronic pancreatitis (CP) patients have been assessed. Serum CRP and IL-6 concentrations were significantly higher in PC than healthy subjects, and increased in patients with advanced stages of tumor [41]. Similar findings have been demonstrated by other authors, who have indicated elevated serum levels of IL-6 and CRP in PC patients in comparison with healthy subjects [50] and increased serum levels in more advanced tumor stage when compared to early stages of PC [51]. Moreover, in our previous study, serum IL-6 and CRP concentrations increased with

tumor size (T factor), the presence of lymph node (N factor), and distant metastases (M factor). The differences were significant for IL-6 levels when T, N and M factors were analyzed and for CRP in the assessment of N factor [41]. Our results were in line with the findings of other authors, who revealed that plasma IL-6 levels increased with higher tumor dimension, but not with nodal involvement [52]. In addition, we previously indicated that the serum levels of IL-6 were significantly higher in non-resectable tumors and in patients who died during the 2-year observation period [41]. Moreover, the area under the receiver operating characteristic curve (AUC) for IL-6 was the highest among all proteins tested in the differentiation between PC and CP as well as between PC and healthy subjects [41]. We also revealed that serum IL-6 was proved as a significant prognostic factor regarding patients' survival, which was confirmed using univariate analysis [41]. Similar results were presented by other authors, who indicated that increased levels of IL-6 might predict unfavorable prognoses in PC patients [53]. In contrast to these results, Bellone et al. [46] failed to indicate any significant differences in serum IL-6 concentrations between PC patients and healthy subjects. The overall findings of multiple authors, as presented here, suggest the usefulness of serum IL-6 and CRP in the diagnosis and prognosis of PC patients as well as in the differentiation of patients with CP.

3.3. Other cytokines – hematopoietic growth factors (HGFs)

Hematopoietic growth factors (HGFs), also known as hematopoietic cytokines (HP), are a group of small secreted proteins that may induce differentiation and proliferation of hematopoietic progenitor cells [19]. Some investigations have proved that the effects of these molecules are not limited to bone marrow cells, but may also stimulate the proliferation of non-hematopoietic and malignant cells [19,54]. Thus, it is suggested that these proteins might play a role in the development of malignant tumors, including PC (Table 2). Selected HGFs, such as granulocyte-colony stimulating factor (G-CSF) and macrophage-colony stimulating factor (M-CSF) are able to stimulate tumorigenesis and growth of malignant cells in an autocrine manner. As a result, endogenous cytokines are produced aberrantly in many malignancies, including PC [19,55]. In addition, several cell lines of malignant tumors are capable of secreting large amounts of these cytokines and expressing their receptors [54,56]. Some investigators proved that PC cells are constitutively capable of producing M-CSF, G-CSF and other HGFs *in vitro* and may enhance the production of extracellular matrix degrading proteinases in response to HGFs [54,56,57]. This may explain a biochemical mechanism that promotes the invasive behavior of malignant cells. Elevated serum levels of selected HGFs in patients with PC have been evaluated in our previous study [56,58–60]. We assessed that serum levels of G-CSF, GM-CSF, M-CSF, CEA and CA 19-9 were significantly higher, while stem cell factor (SCF) was significantly lower in PC patients when compared to healthy subjects [56,58–60]. Our findings were in line with the study by Vasiliades et al. [61], who also indicated that SCF levels were significantly lower, while M-CSF levels were significantly higher in PC patients than in healthy controls. No significant difference was found for GM-CSF levels. However, these findings suggest that these cytokines are produced by malignant cells.

Table 2
Selected cytokines involved in the development of pancreatic cancer.

Cytokine	Abbreviation	References
Interleukin 6	IL-6	[41,46,47,50–53]
Interleukin 3	IL-3	[58,61]
Macrophage colony-stimulating factor	M-CSF	[56–60]
Granulocyte colony-stimulating factor	G-CSF	[56–58]
Granulocyte-macrophage colony-stimulating factor	GM-CSF	[57,58,61]
Stem cell factor	SCF	[58–61]

The study by Vasiliades et al. [61] demonstrated that there are significant positive correlations between the serum levels of CEA and M-CSF, between GM-CSF and SCF, and between GM-CSF and IL-3. Similar results were established in our previous study, where the significant correlation between M-CSF and CEA was determined [56]. Moreover, some clinical investigations have assessed the diagnostic characteristics of selected HGFs in PC [61]. The diagnostic sensitivity of M-CSF levels was higher than for SCF and IL-3 [61]. In our previous study, the percentage of elevated concentrations of M-CSF was higher than G-CSF, but lower compared to classical tumor markers. This percentage increased, however, to 84% for combined analysis of M-CSF with CA 19-9 [56]. Our previous study revealed that the AUC for M-CSF was higher than for G-CSF, but lower than for CA 19-9 and CEA [56]. Similar results have been presented by other authors, who have also indicated that the AUC for M-CSF was higher than for GM-CSF, SCF, IL-3, and CEA but lower than for CA 19-9 [61]. In addition, our previous study has demonstrated that tumor stage, presence of nodal and distant metastases, tumor resectability and serum levels of M-CSF were significant factors affecting overall survival. However, multivariate regression analysis with the Cox proportional hazard model revealed that only TNM stage, presence of distant metastases and tumor resectability were independent prognostic factors for PC patients' survival [56]. In conclusion, presented findings confirm the potential significance of selected HGFs, especially M-CSF, in the diagnosis and prognosis of PC patients.

3.4. Matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs)

MMPs are a large family of structurally related endopeptidases that are able to degrade the basement membrane and extracellular matrix components. It has been found that several MMPs, especially gelatinases such as metalloproteinase 9 (MMP-9) and metalloproteinase 2 (MMP-2), play an important role in the development of various malignancies via promotion of invasion, metastasis, growth, cell migration, and angiogenesis [62]. MMPs are produced by various cells, such as macrophages, leukocytes, endothelial cells and fibroblasts, as well as tumor cells [63]. The proteolytic activity of MMPs is strictly regulated via their tissue inhibitors (TIMPs). The imbalance between MMPs and TIMPs is critical in the development of various malignancies, including PC (Table 3) [62,64]. It has been shown that MMP-9 expression is associated with degree of tumor cell invasiveness, thus the ability to upregulate MMP-9 expression may simplify the invasion of PC cells [21]. Moreover, some clinical investigations have revealed that overexpression of MMP-9 is associated with elevated levels of its tissue inhibitor [65,66]. However, little is known about MMP-9 and TIMP-1 serum levels in patients with PC and their possible significance as tumor biomarkers for PC. Thus, in our previous study, we assessed the serum concentrations of MMP-9 and its tissue inhibitor in PC patients and compared those levels with classical tumor markers for PC (CA 19-9 and CEA). We revealed that serum levels of MMP-9 and TIMP-1 in PC patients were significantly higher than in patients with CP and healthy subjects, which is similar to classical tumor markers [67]. Moreover, we demonstrated that the serum levels of the protein tested increased with more advanced stages of disease. In the study by Pezzilli et al. [68], the authors assessed the serum concentrations of another gelatinase –

Table 3
Selected matrix metalloproteinases and tissue inhibitors of metalloproteinases involved in the development of pancreatic cancer.

Matrix metalloproteinase	Other name	References
Metalloproteinase 2 (MMP-2)	Gelatinase-A	[68]
Metalloproteinase 7 (MMP-7)	Matrilysin	[69]
Metalloproteinase 9 (MMP-9)	Gelatinase-B	[67]
Tissue inhibitor of metalloproteinase 1 (TIMP-1)	Human collagenase inhibitor (HCI)	[67]

MMP-2 – in PC patients, however they failed to indicate the statistically significant difference between serum MMP-2 levels in PC patients and healthy controls. The diagnostic sensitivity and the AUC for TIMP-1 were higher than for MMP-9 and classical tumor markers. We also revealed that the elevated preoperative concentration of MMP-9 was a significant independent prognostic factor for patients' survival [67]. Our findings indicate a potential clinical significance of serum TIMP-1 and MMP-9 measurements in the diagnosis and prognosis of patients with PC [67]. It is suggested that elevated serum matrix metalloproteinase 7 (MMP-7) is associated with metastatic PC, thus Wang et al. [69] assessed the preoperative MMP-7 levels in patients with resectable PC. The authors indicated that serum MMP-7 levels were significantly higher in patients who had higher T stage, nodal involvement, vascular invasion, moderate/poor differentiation, and advanced stage of disease, which may suggest that serum MMP-7 is highly predictive of unresectable disease and nodal involvement and should be further evaluated as a biomarker to risk-stratify PC patients prior to operation [69]. These findings suggest the potential significance of selected MMPs and their tissue inhibitors in PC.

4. Discussion

The great challenge of future medicine is to explore non-invasive biomarkers, which will be measured in biofluids, such as blood or urine using easy to perform, cheap and accurate methods. Thus, the establishment of specific, biochemical markers is sorely needed to improve the management of PC patients. It has been proved that selected inflammatory mediators, such as cytokines and specific inflammatory proteins such as CRP, as well as various MMPs and TIMPs might be involved in tumor progression, such as cell growth, proliferation, migration and angiogenesis of tumor cells, including PC.

For the future of medicine, novel and accurate biomarkers are crucial, so that this malignant disease can be detected at an early stage. Many researchers have focused on molecular mechanisms of PC progression. Exosomes are multivesicular body-derived vesicles released by various cell types that might serve as message carriers during communication as well as during cancer-genesis and cancer-related immune reactions. The authors suggest that proteomics, identification and quantification of proteins (the proteome) of a biological fluid or cell at a specific point in time, might be a promising technique to discover potential, novel biomarkers for early cancer detection. Thus, extensive research on pancreatic cancer-derived exosomes is sorely needed [70,71].

4.1. Limitations of the study

Although various authors suggest the potential usefulness of particular biomarkers in the diagnosis of PC patients, in routine practice there are no markers useful in the early detection of PC. The first limitation is wide heterogeneity of the analyzed population, such as age, gender, coexisting conditions or methods of analysis. In addition, due to the non-specific nature of presented biomarkers for cancer, the diagnostic value of these proteins may be limited. However, further investigations with larger validations and populations are sorely needed to clarify the diagnostic and prognostic significance of these proteins in PC.

5. Conclusion

Our review presents a number of research papers, where various authors evaluated the diagnostic and prognostic significance of selected HGFs, especially M-CSF as well as CRP and IL-6 in PC patients in comparison to well-established tumor markers for this malignancy. In addition, selected chemokines, MMPs and their tissue inhibitors may play an important role in the pathogenesis of PC.

Conflict of interest

The authors declare no conflict of interests.

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The author contribution

Study Design: Ala Litman-Zawadzka, Marta Łukaszewicz-Zając, Barbara Mroczko

Data Collection: n/a

Statistical Analysis: n/a

Data Interpretation: n/a

Manuscript Preparation: Ala Litman-Zawadzka, Marta Łukaszewicz-Zając, Barbara Mroczko

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