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An Insight to Biomarkers for Pancreatic Ductal Adenocarcinoma

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KEYWORDS

PDAC, biomarker, OPN, saliva biomarker, pancreatic juice biomarker, stool biomarker

ABSTRACT:

Introduction: Pancreatic Ductal Adeno Carcinoma (PDAC) is most devastating tumour destroying human life in recent times. The lethal nature of this aggressive disease is shown by the fact that incidence rate and mortality rate are almost equivalent to each other.

Objective: This review exhibits an effective look towards advanced biomarkers having potential to redeem the shortcomings of a traditionally used CA 19-9 and CEA. CA 19-9 and CEA are used routinely for prognosis. It is the biomarker accepted by the FDA, for PDAC despite this it fails to serve as a benchmark for biomarkers, the robustness being the severe issue including the drawbacks like lack of specificity and sensitivity, absence of expression in Lewis negative phenotype and higher false positive increase observed in obstructive jaundice.

Results: Thus, this review aims to throw light to the new and exciting areas of biomarkers present in serum, saliva, pancreatic juice, stool marker which are likely on the horizon. In this literature we have peaked at glance on various kinds of biomarkers and to make differentiation between them i.e. diagnostic, prognostic and predictive.

1. Introduction

Point-of-care-testing (POCT or bedside testing) is referred as a medical diagnostic testing at or near the point of care-that is, at the time and place of patient. Point of care diagnosis is very essential as well as beneficial for the patients who have major disease for e.g. cancer, stroke etc. Point-of-care diagnostics (POCD) lead to a reduction in cancer-related deaths. As we all know that in day today life, the ratio of Cancer is increasing rapidly thus the point of care testing (1) helps the patients for early stage diagnosis at bedside and then he or she can reach the prescribed doctor or a specialist for optimal treatment for such problem. Thus, the point of care testing or bedside testing prevents the patients from the dangerous disease at an early stage. Point of care testing or bedside testing will only be effective or ideal if it is cost-effective, rapid, reliable, and functional without excessive prior-processing of samples, non-invasive diagnostic tools highly sensitive for detection of cancer at an early stage (2). The device makes easy of self-use or use by a general physician or nurse at the point of care. Results obtain from point-of-care tests should be precise, sensitive, and generated rapidly to assist in the selection of the best course of treatment for patient. It gives fast medical decisions, as the cancer can be diagnosed at an early stage, leading to improved health outcomes for patients by enabling the early start of treatment. There is an upcoming trend for the implementation of POCT into established clinical practice. POCD, the tests need to be simplified, which reduces the overall cost of materials, equipment, and personnel costs. POCD would enable rapid clinical decision-making in the diagnosis, which would considerably improve patient outcome by providing treatment and medical intervention at an early stage. There is an emerging need for the development of POCT devices that could use for early diagnosis of diseases. The biomarker is the most important component of POCT, for the bioanalytical performance of an assay. Also, there are several prospective technologies, e.g., microfluidics, lab-on-a-chip technologies, system integration, device automation, and signal readout etc. The use of “lab-on-a-chip” and biomarker technologies, so that a test that was once laboratory-based is now portable and fit-for-use by the patients themselves or by on-site medical staff. Therefore, biomarker should have great potential to detect changes in the disease state of an individual. This can be achieved by detecting aberrations in Patient’s sample present in serum, saliva, pancreatic juice, stool marker for early diagnosis of cancer.

Pancreatic ductal adenocarcinoma is widely observed kind of pancreatic cancer. It is fatal disease and may lead to survival for less than a year. PDAC will become second most fatal cancer up to 2020 in the developed

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countries (3). PDAC has three key precursors neoplasms: intraepithelial neoplasia (PanIN), intraductal papillary mucinous neoplasm (IPMN) and mucinous cystic neoplasms (MCN) (4). PC is majorly marked by rapid progression, extremely poor prognosis and aggressive behaviour. Pancreatic cancer increases incidence and aggressiveness, has become a major challenge for clinical management and researcher. Diagnosis of PDAC has become a very difficult task due to the lack of specific symptoms and thus diagnosis can only take place after the tumor has metastasized. The poor prognosis of PDAC had resulted in late-stage detection which is one of the vulnerable reasons leading to poor survival of patient. The ineffectiveness of established techniques for early detection contributes to poor diagnosis. The inability to detect pancreatic cancer in its early treatable stage is a vital problem. To overcome that, Biomarker is used for early detection of Pancreatic Cancer. To develop non-invasive tests is the basic goal of biomarker in order to detect the cancer in earlier state so that survival rate can be increases to greater extent. Recently, CA19-9 is the only biomarker approved by FDA and utilized in the routine management of pancreatic cancer. Even though many novel candidate biomarkers have been proposed for earlier diagnosis, none have been implemented into routine practice. A research work is going on for developing candidate markers, since there being no specific tumor marker for PDAC diagnosis. In this review, the aim is to find a new exciting pancreatic cancer biomarkers present in various biological fluids such as serum, pancreatic juice, saliva and stool.

2. Aetiology

According to the recent data mostly men are diagnosed with PC than women (5). Risk of developing PDAC is more susceptible with age, almost all patients who develop PC are older than 45. Especially black people are more vulnerable than Asian, Hispanic or white people to develop PC. Several suspected risk factors associated with PDAC are cigarette smoking explicitly promoted generation of Granulocyte Macrophage Colony Stimulating Factor (GM-CSF), obesity, chronic pancreatitis, genetics, and physical inactivity also diet(high fat and protein, high calorie, coffee, low fruit and vegetable intake). Chronic and heavy alcohol consumption are risk factors which increases the chances of pancreatic cancer (6, 7, 8 and 9). Occupational exposure to pesticides, benzene, certain dyes, nickel and petrochemicals, Helicobacter pylori, and Hepatitis B virus increases chances of pancreatic cancer (6). The most observed manifestation/ sign are painless progressive jaundice, bloating, abdominal pain, anorexia, steatorrhea, vomiting, weight loss and acute onset of diabetes (10). Early PDAC is not characterized because of absence of symptoms.

3. Investigation

The determination of PC is a lengthy process which may comprise of following advances. Imaging technique consisting of Transabdominal Ultrasonography (USG), Magnetic resonance imaging (MRI), Dual phase spiral Computed tomography(CT), MR Cholangiopancreatography (MRCP), Endoscopic ultrasound(EUS), fluorodeoxyglucose positron emission tomography(FDG-PET),Laparoscopy, Endoscopic retrograde Cholangiopancreatography(ERCP) (5, 11). Ultrasonography, which can identify pancreatic tumors, dilated bile ducts and liver metastases, and exclude the presence of CBD stones. Dual-phase spiral computed tomography (CT) accurately predicts resectability in 80-90% of cases. Magnetic resonance (MR) imaging detects and predicts resectability with accuracies similar to CT. MR Cholangiopancreatography (MRCP) provides detailed ductal images without risking the complications incurred by Endoscopic Retrograde Cholangiopancreatography (ERCP). ERCP can confirm the typical ‘double duct sign’ (adjacent strictures in the bile duct and main pancreatic duct) and provides the opportunity for aspiration, brushings or biopsies of the bile duct system. Endoscopic Ultrasonography is highly sensitive for detecting small tumors that are equivocal on CT, and assessing vascular invasion, and provides a further opportunity for biopsy. Positron emission tomography is mainly used for demonstrating occult metastases, although it is important to remember that hyperglycemia can produce false-negative results because the chosen radiotracer is a glucose analogue. Laparoscopy, including laparoscopic ultrasound, can detect occult metastatic lesions of the liver and peritoneal cavity not identified by other imaging modalities. Preoperative biopsy should be performed to confirm the diagnosis in patients who are suitable only for palliative treatment. These imaging parameters are costly, potentially invasive and time consuming; they are usually performed only after the onset of symptoms.

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4. Biomarker

In the words of The National Cancer Institute (NCI) "Biological Marker i.e. Biomarker is biological molecule found in blood and, body fluids such as pancreatic juice, saliva this biomolecule is measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" (12, 13). A Biomarker can be categorised into three primary ways (13, 14). They are as follows:

i. Diagnostic: - It detects diseases onset, recurrence or progression for identifying early stage cancer (13, 15).
ii. Prognostic: - To forecast the developmental stages of disease, for determining a patient's ability to survive in the lack of treatment (13, 15).
iii. Predictive: - To foresee the response of patient to treatment (13, 15).

A Biomarker is a molecular or a process-based change that indicates the position of underlying malignancy. The Primary function of the biomarkers is in the diagnosis of cancer and to assess the effect of chemotherapy other functions are to determine prognosis and to predict tumour recurrence. Constantly they are being explored to drive patient management, either by identifying patients who do not require any, or any further treatment. A biomarker is known as an ideal biomarker when it would permit the early diagnosis of cancer in its budding stage (16). The main factor affecting the dismal fatal tumour is its late stage identification causing many to lose their lives. Thus biomarker can serve as a lifeline for PC patients. Due to their low cost, and minimal invasiveness, biomarkers remain an ideal method to detect PDAC in its early stages. This leads to the urgent need of biomarkers that can help to detect PDAC at an early stage in pancreatic patients and improve the survival of pancreatic cancer patients. For this we have gold standard CA 19-9 biomarker approved by FDA, still we need to think out of box. Thus many new and alternative approaches for biomarkers have been put forward in this review. This review focuses on the most widely used emerging novel Potential PDAC biomarker for Pancreatic Cancer.

5. Serum biomarker

Carbohydrate Antigen 19-9(CA 19-9) is monosialoganglioside, also called as mucinase sialylated lewis (a) antigen discovered in 1981monoclonal antibodies obtain from mice immunized with human colorectal carcinoma cell line (17, 18). Literature review revealed that sensitivity being 79% while specificity is 82%. Upregulation of CA 19-9 (>37U/Ml) is related with gastrointestinal carcinomas especially pancreatic cancer.

CEA is glycoprotein found by Gold and Freedman in 1965 (19). By 13 published reports on 1323 patients CEA shows sensitivity of 54% and specificity of 79% (20). Carbohydrate Antigen 19-9(CA19-9) and Carcinoembryonic Antigen (CEA) has been routinely used for prognosis and is the only biomarker approved by the FDA, despite this it fails to serve as a benchmark for biomarkers and does not prove as useful as expected reason being the low specificity and sensitivity in early stages of the PC(10).

6. Novel biomarkers present in serum

1.0 Regenerating islet-derived protein (REG)

Regenerating islet-derived protein (REG) is a calcium dependent lectins protein that are responsible for cell differentiation and proliferation (21). REG is increased in gastrointestinal malignancies and in various inflammatory bowel diseases (22). The REG family consist of proteins which are known to play vital role in tissue regeneration and inflammation in digestive organs. Five REG family members have been explored which includeReg1A, Reg1B, Reg3A, Reg3G and Reg4. REG1A gene in PC is overexpressed and it is due to increased cell proliferation and tumor growth, by in vivo and in vitro (23). Patients with PDAC have elevated level of Reg1A and Reg1B than healthy individual.Pancreatitis associated gene subfamily REG3 include REG3A and REG3G. These proteins are activated in response to inflammatory stimuli (24). Reg3A having accelerated PC cell growth in response to IL-6 via JAK2/STAT3 signalling pathway (25, 26). Acinar-to-ductal metaplasia (ADM) and pancreatic intraepithelial neoplasia (panIN) are precursor for development of PDAC. Reg1A and Reg 3A/G are highly elevated in ADM tissue. Reg3A leads to formation of ADM with concurrent activation of mitogen activated protein kinase in acinar cells by using culture in mouse.

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ADM is concern about Trans formation of acinar cell to ductal cell phenotypes. It is marked by formation of duct like structures. Elevated expression of ductal biomarker such as cytokeratin 19(CK19) while decreased expression of acinar biomarker such as amylase (27). Screening of all Reg protein in PC patient as well as healthy individual is done. No expression of Reg1A and Reg3A/G are observed in normal acini and ducts while in PC subject's positive duct like structure observed near tumor area. To confirm ductal phenotypes the Reg1A is co-stained with CK19 using immunofluorescence and confirms structure with ADM (28). REG-4 is the most recently invented gene in the family (29). It is observed to be increase in PDAC and therefore can be consider using as diagnostic biomarker for same. R.Takayama et.al has studied this with 92 subjects with pancreatic cancer, 28 patients with pancreatic tumour, 11 patients with pancreatitis and 69 healthy controls using Standard Sandwich ELISA technique and revealed serum level of REG4 is higher in pancreatic cancer patients($P < 0.001$) while in patients with pancreatitis ($P < 0.001$). Receiver Operating Characteristics (ROC) reported that serum REG4 performed well as compared to serum CA 19-9 for differentiating patients with pancreatic cancer and others as healthy controls [area under the curve (AUC) for REG4 and CA 19-9 are 0.922 and 0.884 respectively. Also for REG4 sensitivity is 94.4%, specificity is 64% and accuracy being 77.5% for the cutoff value of 3.49ng/ml.

2.0 Osteopontin (OPN):

Osteopontin is a sialic acid-rich, non-collagenous, matricellular phosphoglycoprotein normally produced and secreted into various biological fluids including serum, plasma, milk and urine (30). It is also known as bone sialoprotein 1, or termed early T-lymphocyte activation (ETA-1) (31, 32). Osteopontin is synthesized by osteoblasts, macrophage, kidney, Activated T-cells and vascular smooth muscle cells (33). It signifies an important role in performing normal physiological processes such as bone resorption, tissue remodeling and vascularization; however, it also carry out various pathophysiological processes like cancer, myocardial necrosis, atherosclerosisas well as chronic inflammation and autoimmune disease (34, 35). It also facilitates neoplastic process like Stimulation of migration and invasion, stimulation of cancer cell proliferation and progression and enhancement of metastatic ability also having in vivo function such as immune and inflammatory response, bone calcification and apotosis. OPN is a key factor in chronic inflammation and autoimmune disease (36). It has been revealed that OPN pursued the inflammation and formation of metastasis by binding to cell surface receptor like CD44 and integrins and can also be used as proinflammatory cytokine, modulating immune responses through elevated expression of cytokines, and synergize signal through EGFR and HGF receptor (37). OPN plays a vital role in many signalling pathways leading to tumor growth, angiogenesis, Proliferation and metastasis in various kinds of malignancy. Cho et al 2008, Mi et al 2009 and Shang et al 2012 showed that increased level of OPN lead to development and progression in breast cancer, cervical cancer, hepatocellular carcinoma and gastric carcinoma (38, 39, and 40). OPN is usually found overexpressed in PC. Brand et al 2011 revealed that increased serum level of OPN could serve as biomarker, for metastatic progression of PDAC. This overexpression can be related to lesser survival rate in pancreatic cancer patients. Koopman et.al compared serum OPN level with CA 19-9 level by utilising ELISA technique and found that OPN diagnostic features outperformed CA19-9, biomarker for PC. The OPN sensitivity is 80% while specificity is 97% (41). Thus OPN is regarded as one of the promising biomarker for PC. Zhivkova- Galunska et al 2010 study reported that OPN responsible for invasion and metastasis in PC cells and this leads to deterioration of tumor (42).

3.0 Carcinoembryonic antigen-related cell adhesion molecules (CEACAMs):

CEACAMs is a transmembrane protein belonging to the Carcinoembryonic antigen immunoglobulin super family with functions in cell adhesion, in intracellular and intercellular signalling, and at the time of complicated biological states likes cancer progression, inflammation, angiogenesis and metastasis. Commonly known CEACAMs are CEACAM1, CEACAM5 and CEACAM6. CEACAMs are considered as a valid biomarker for PDAC detection (43). CEACAM1 is also called as biliary glycoprotein-1, CD66a (cluster of differentiation 66a), pp120 and C-CAM1 (44). These are expressed on the surface of human granulocytes, lymphocytes, endothelia as well as in epithelial cells (45). CEACAM1 is found in different cancer types like pancreatic endocrine tumors, breast and bladder.

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Simeone et al first explain CEACAM1 in pancreatic adenocarcinoma by gene expression analysis and by identification of CEACAM mRNA (45). Further CEACAM was explained by Fiedler et al to distinguish cancer patient from controls highlighting a sensitivity of 85% and specificity of 90%.

4.0 Matrix Metalloproteinase 7(MMP7):

Matrix Metalloproteinase 7 is epithelium derived member of family zinc dependent endopeptidases, which contribute in tissue remodelling and stimulate neovascularization (both in physiological and pathological processes such as tumours) and inflammatory response (46). It also regulates vascular stability and permeability in response to tissue injury (47). MMPs are produced by Leukocytes, Macrophages and Connective tissue cells (48). It is elevated in 4th Stage in PDAC patients. It is observed to be elevated in several malignancies like bladder, ovarian, prostate, renal cell and bile duct cancer. MMP2 present in tumor cells and stroma (53.17 and 79.31% respectively while absent in normal pancreas (96.55%). Giannopoulos et al shows presence of MMP2 in cancer cell in PDAC (49). Wang et al 2016 found that MMP7 is use as distinct tool to forecast nodal involvement and unresectability having (AUC=0.68) in his study. He measured Serum MMP7 level by using sandwich enzyme linked immunosorbent assay method. ROC curve was plotted to check MMP7 as a Prognostic biomarker for PDAC. The AUC Curve of MMP7 was (AUC=0.68, 95% CI 0.57-0.79) While ROC curve for CA 19-9 having (AUC=0.57, 95% CI 0.40-0.73) (50). Recurrence time of diseases in Patient having high level of MMP7 who underwent RO resection is near about five month while ten month for patients having low level of MMP7 in serum. Median value of MMP7 was 7.0 ng/mL having range 1.7-33.0 ng/mL. Also various study reported that serum MMP7 is higher in patients with Nodal involvement (P=0.02), T stage (P=0.04), Vascular invasion (P=0.006), Moderate/ poor differentiation (P=0.04) and advance disease (P=0.006). MMP7 observed in tumor cell (96.55%) and less in stromal cells (55.17%) than compared to normal pancreas (93.10%).

5.0 Macrophage Inhibitory Cytokines 1(MIC-1):

Macrophage Inhibitory Cytokines 1(MIC-1) is an autocrine regulatory molecule, which belong to the transforming growth factor beta (TGF-β) super family of cytokines. It is found in activated macrophage, prostate, adipose tissue and in lesser amount in kidney, liver and brain. MIC-1 is up regulated in various pathological processes such as acute injury, inflammation, and caner (such as pancreatic, prostate, breast, colon and melanoma) also it is over expressed in malignant tumours (51). Thus serum level of MIC-1 might be a novel diagnostic biomarker for early detection of PC. MIC-1 is also used as an anticancer, as it is promoter region is target of p53. Koopman et al revealed that MIC-1 outperform in all serum biomarker including CA 19-9 biomarker by using gene expression study and in-situ hybridization. He differentiate between healthy and patients with pancreatic cancer (52, 53, 54). Also Ozkan et al, 2011 revealed that serum MIC-1 level elevated in patients with pancreatic cancer than in benign pancreatobiliary diseases and healthy individual($P<0.05$).MIC-1 has same sensitivity (81%) as like as CA 19-9 but having lower specificity (73vs. 97%) in PC subjects. Also increased in benign biliary diseases than in healthy individual i.e. P value for CA 19-9 is 0.024 while MIC-1 having P value 0.036 (55).

Pancreatic juice

Pancreatic juice is regarded as an exceptionally rich source tumour-associated proteins and mutant DNA, with associated genetic changes release from pancreatic cancer cell. Assessment of PJ can provide opportunity to find biomarker for early stage detection of PC thus it serves as an ideal specimen for detection of PC. It has been revealed that various biomarkers have been identified in pancreatic juice like Exosomes, Proteomic, DUPAN, and Cathepsin E.

Exosomes are endocytic and heterogeneous small membrane vesicles. They have cup-shape structure with 30-100nm in diameter, which are released from various cell types having vital role in Intracellular Communication, Biological events and in Cancer Development, i.e. Metastasis and observed in various body fluids like Saliva, Serum or Plasma, Urine and Breast milk (56,57,58,59,60,61 and 62). Exosomes plays vital role in tumour initiation and growth with mechanisms such as induction of apoptosis of activated CD8+, T cells and suppression of natural killer cells activity (63, 64). S. Nakamura et.al have studied 35 subjects underwent Enhanced Recovery Programme and subsequent collection of PJ samples out of which 27

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patients had PDAC and 8 patients had chronic pancreatitis (CP) and it is used as biomarker.

MicroRNAs which are small, noncoding ribonucleic acids involved in posttranscriptional gene regulation by either degrading or blocking the translation of mRNA targets. miRNAs plays vital role in various cellular functions, circulating miRNAs corresponds with development and progression of cancer. Thus, MicroRNA has also been considered as effective biomarkers for PDAC. Wang et.al has used microarrays and qRT-PCR to quantify miRNAs in Pancreatic Juice and explored that miR-205, miR-210, miR-492 and miR-1247 levels have been elevated in PDAC patients with specificity 88% and sensitivity being 87% (65). Szafranska et al reported that miR-216 and miR-217 are down regulated in tumour than control. Expression of miRNA-196 and miRNA-196a are elevated in pancreatic cancer patient than normal individual while also Up regulation of miR-221 in PC leads to distant metastasis (66). Xu et al revealed two miRNAs (miR 486-5p and miR-938) used as diagnostic biomarker to differentiate between PDAC and Control, miR-486-5p used as diagnostic biomarker with AUC value 0.861 and 0.707 for PDAC and normal individual respectively (67). The expression level of miR-22-3p, miR-64-2b-3p, miR-88s-5p and CA 19-9 are up regulated in PDAC patients in early stages.

Saliva

Saliva is regarded as an indicator of a dynamic state of health and disease in humans. Saliva indicates interesting features as a fluid for screening and diagnosis of PC. Since saliva sampling is simple, cost effective & convenient thus Saliva sample can act as ideal biomarker for PC detection (68). Saliva contains many biological constituent which are proteins, nucleic acid, hormones and various type of microorganism. It also contains promising biomarker for PDAC such as Metabolome, Transcriptome and Microbiome (69).

1.0 Metabolome:

Sugimoto et al, 2010 studied Metabolome using Capillary Electrophoresis Time of flight Mass Spectrophotometry (CE-TOF-MS) detection method which revealed an important contribution of eight metabolites in detecting PC through non-invasive means of saliva. Sample obtains from Pancreatic, Oral, Breast and Periodontal disease patients and healthy controls. Under this for PC he identified, eight metabolite out of which five are essentials namely leucine, isoleucine, tryptophan, valine and phenylalanine and other three being supplementary glutamic acid, glutamine and aspartic acid to our body mechanism. Decreased level of leucine, isoleucine, tryptophan, valine and phenylalanine in PC Subjects. The ability of metabolite to discriminate sample and control studied by Receiver Operator characteristics curve (AUCs) was 0.933 (70).

2.0 Transcriptome:

A better and more stable source of biomarker have been identified in the saliva supernatant i.e. Transcriptome Zhang et al made it possible to distinguish between healthy and patients with PC He analysed messenger RNA (mRNA) which are KRAS, MBD312, ACRV1, and DPM1 in saliva supernatant. He used 30 chronic pancreatitis and 30 healthy subjects using Microarray and qPCR detection method (AUC=0.971, 95%, CL=0.911-0.994, P< 0.001, Se=90%, Sp=95%) (71). To overcome the drawback of study of Zhang et al a major light has been thrown by the study of Liu et al. He identified 29 new saliva mRNA from 516 genes which prove more helpful because of better sensitivity (Se=92%) than four mRNAs (72). Xie et al studied on Twenty Benign Pancreatic Tumour (BPT) and Forty Healthy control by using microarray and qPCR. He shows that two saliva miRNAs (mi3679-5p and miR-940) distinguishes resectable PC and healthy individual (with Se=72.5%, Sp=70%) and patients with BPT (having Se=62.5%, Sp=80%), patients without cancer (Se=70%, Sp=70%) (73). Thus, saliva miRNAs evaluation could be novel biomarker for PC detection.

3.0 Microbiota

Another stable source of biomarker in saliva is Microbiome genome coded by the microbiota. Microbiota are varied example presence of certain germ such as porphyromonas gingivalis and Aggregatibacter actinomycetemcomitans increases risk of pancreatic cancer while decreases risk in presence of fusobacterium genus and leptotrichia species in saliva sample. Farrell et al on twenty-seven CP Patients and twenty-eight healthy by using microarray and qPCR, the combination of granulicatella adicanes and streptococcus mitis are able to differentiate between PC and healthy individual with Se=86%, Sp=83% and AUC=0.68,95%, Cl=0.57-0.78,

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P=0.0063 while association of N.elongata and S.mitis distinguishes between PC and healthy control with AUC=0.90, 95%, Cl=0.78-0.96, P<0.0001 having Se=95% and Sp=82% (74).Fan et al revealed that P.gingivalis (OR=1.60, 95%, Cl=1.15-2.22) and A. Actinomycetemcomitans (OR=2.20, 95%, Cl=1.16-2.18)increases risk of PC while Fusobacterium (OR=0.94, 95%, Cl=0.89-0.99) and Leptorichia (OR=0.87, 95%, Cl=0.79-0.95)by using sequencing of the rRNA 16s (75). Torres et al study shows that ratio of Leptotrichia/ porphyromonas (L/P) was significantly higher in PC patients than control, (p= 0.001), while Neisseria (P=0.07) and Aggregatibacter (P=0.09) having lower abundance (76).

Inflammatory mediators

An Inflammatory Mediators is a messenger which acts on blood vessels or cells to promote an inflammatory response. Inflammatory mediators that contribute to neoplasia include cytokines, Hematopoietic growth factor (HGFs), IL-6, IL-8, and TNF-alfa. Chronic inflammation is an important element playing a important role in the growth of various malignancies including PC. It has been shown by various studies that several inflammatory mediators might be responsible in tumour progression such as growth, proliferation, migration and angiogenesis of tumour cell. Thus inflammatory mediators might be helpful in the screening of PC with the motto of improving the prognosis for PC subjects. It includes (1) Cytokines, (2) Hematopoietic growth factor (HGFs) (3) Interleukin (IL) (77) etc.

1.0 Cytokines (Chemokines):

Chemokines are chemotactic cytokines which are having low molecular weight. These control various physiological processes such as inflammation, infection, immunological response and tissue injury reactions (78). It has been revealed that certain chemokines and their specific receptor might be responsible for the pathogenesis of PC. CXC chemokine regulate tumour progression such as proliferation, growth, angiogenesis and metastasis of cell (79). CXCL-1, CXCL-5, CXCL-8 and CXCL-12 are over expressed in PC cells than normal tissue (80). CXCL-1 and CXCL-8 might be effective markers in indicating prognosis and screening disease progression in PC patients. Subjects with PC having positive CXCL-1, CXCL-5 and CXCL-8 expression had relatively lesser survival compared to those who have negative expression of these proteins.CXCL-1 in PC related with TNM Stage and CXCL-8, cytokine produced by stromal cell and malignant cell and were higher in PC subjects. Also, CXCL-5 level are higher in PC with poorer tumour differentiation while CXCL-7were decreased in PC (81). CXCL12 and CXCR4protein receptor of CXC Chemokine ligand 12, over expression of CXCR4 in resected PDAC leads to shorter survival (82).

2.0 Hematopoietic growth factor (HGFs):

Pancreatic Cancer Cell is naturally having a potential to produce Hematopoietic growth factor (HGFs) such as M-CSF (Macrophage-Colony Stimulating Factor), G-CSF (Granulocyte-Colony Stimulating Factor) and other HGFs in-vitro. Hematopoietic growth factor (HGFs) consequences of these molecules is not only on bone marrow but also stimulate the proliferation of non-hematopoietic and malignant cells (83, 84), .Macrophage-Colony Stimulating Factor (M-CSF) level have been elevated in PC patients while Granulocyte-Colony Stimulating Factor (G-CSF) have no significant changes (85). Thus M-CSF served as a diagnosis and prognosis of PC.

3.0 Interleukin-6(IL-6)

Interleukin-6 is a proinflammatory cytokine that induce apoptosis to tumour cells (86). IL-6 serves as a connector that joins inflammation and angiogenesis to malignancy. Serum level of IL-6, IL-8, and TNF-alfa get elevated compared to other control groups (87). Also, serum interleukin-6(IL-6) and C-Reactive Protein(CRP) level elevated in PC patients with Tumour size(T-factor), Presence of lymph node(N-factor) and Distant metastases(M-factor) (88, 89).

Stool biomarkers

The de-epithelization or shedding of duct epithelium, from which pancreatic cancer arises, can be used to predict mutations or genetic changes related with PC like mutant K-RAS and p53 (16). K-ras activating point mutation in codon 12 and p53 tumour cell suppressor gene mutation are abnormalities in PC Patients (90). Xing Hua LU et.al identified in his study Fecal K-RAS and p53 as a prominent biomarker for PC. In this study he utilised PCR-restriction fragment length polymorphism (PCR-RELP) for Faecal K-ras and PCR-

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single strand conformational polymorphism (PCR-SSCP) for p53. For this he studied 31 Faecal samples from subjects and 85 controls for gene mutation analysis, and he found that sensitivity and specificity for Faecal k-ras was 77.4% and 81.2% respectively while sensitivity and specificity of Faecal p53 was 25.8% and 95.3% respectively (91). Uehara et al assumed that Faecal K-ras mutation was related with dysplasia of epithelial lesion, which shows high risk of pancreatic cancer. The objective of faecal k-ras is to screen patients with risk of pancreatic cancer.

Conclusion

In this article the detailed description of biomarker for PDAC is mentioned which include biomarker from serum, OPN, CEACAMs, MMP7, MIC-1, Pancreatic juice, saliva, Inflammatory mediators and stool biomarkers etc were discussed. These biomarkers may be explored for diagnosis as well as prognosis of PDAC.

Future perspective

Diagnosis of PDAC has become a very lengthy and difficult task due to the lack of specific symptoms and thus diagnosis can only take place after the tumor has metastasized. The inability to detect pancreatic cancer in its early treatable stage is a vital problem. To treat it, is a further major challenge for clinical management and researcher. Pancreatic cancer having a multifactorial pathophysiology, focus shall be given on developing a sensitive and specific biomarker in addition with improvements in method of early-stage diagnosis. Early detection of cancer greatly increases the chances for effective treatment and survival rate of PC patients. This review provides an insight to the novel biomarkers for the early detection of pancreatic cancer. Various types of biomarkers have been identified for the detection of pancreatic cancer and shown great opportunity for the early diagnosis of pancreatic cancer. It requires validation. Another challenge to use described biomarkers for the early detection of pancreatic cancer is the specificity and sensitivity for the diagnosis. Novel biomarkers may provide a better specificity and sensitivity.

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