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REVIEW

Chromodomain-helicase-DNA binding protein 5, 7 and pronecrotic mixed lineage kinase domain-like protein serve as potential prognostic biomarkers in patients with resected pancreatic adenocarcinomas

Crystal S Seldon, Lauren E Colbert, William A Hall, Sarah B Fisher, David S Yu, Jerome C Landry

Crystal S Seldon, David S Yu, Jerome C Landry, Department of Radiation Oncology, Winship Cancer Institute, Emory University School of Medicine, Atlanta, GA 30322, United States

Lauren E Colbert, Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY 10065, United States

William A Hall, Department of Radiation Oncology, the Medial College of Wisconsin, Milwaukee, WI 53226, United States

Sarah B Fisher, Division of Surgical Oncology, Department of Surgery, Emory University School of Medicine, Atlanta, GA 30322, United States

Author contributions: Seldon CS wrote the paper; Colbert LE, Hall WA, Fisher SB, Yu DS and Landry JC equally contributed to this paper with data collection, design, review, editing and approval of the final version.

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Correspondence to: Jerome C Landry, MD, MBA, Assistant Professor, Department of Radiation Oncology, Winship Cancer Institute, Emory University School of Medicine, 1365 Clifton Road, NE, Suite C3008, Atlanta, GA 30322, United States. jland01@emory.edu
Telephone: +1-404-6166349
Fax: +1-404-6166380

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Abstract

Pancreatic cancer is one of the deadliest cancers with a very poor prognosis. Recently, there has been a significant increase in research directed towards identifying potential biomarkers that can be used to diagnose and provide prognostic information for pancreatic cancer. These markers can be used clinically to optimize and personalize therapy for individual patients. In this review, we focused on 3 biomarkers involved in the DNA damage response pathway and the necroptosis pathway: Chromodomain-helicase-DNA binding protein 5, chromodomain-helicase-DNA binding protein 7, and mixed lineage kinase domain-like protein. The aim of this article is to review present literature provided for these biomarkers and current studies in which their effectiveness as prognostic biomarkers are analyzed in order to determine their future use as biomarkers in clinical medicine. Based on the data presented, these biomarkers warrant further investigation,

and should be validated in future studies.

Key words: Chromodomain-helicase-DNA binding protein 5; Chromodomain-helicase-DNA binding protein 7; Mixed lineage kinase domain-like protein; Pancreatic adenocarcinoma; Biomarker

Core tip: Pancreatic cancer is one of the deadliest cancers with a very poor prognosis. Recently, there has been a significant increase in studies and research directed towards identifying potential biomarkers that can be used to diagnose and provide prognostic information for pancreatic cancer. We focused on 3 biomarkers involved in the DNA damage response pathway and the necroptosis pathway: Chromodomain-helicase-DNA binding protein 5, chromodomain-helicase-DNA binding protein 7, and mixed lineage kinase domain-like protein. Based on the data presented, these biomarkers warrant further investigation.

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INTRODUCTION

With an estimated 39590 deaths in 2014, pancreatic cancer is the fourth leading cause of death from cancer in the United States[1]. Pancreatic adenocarcinoma (PAC), the most common type of pancreatic cancer, has a very poor prognosis with a five-year survival rate of 5% for patients with all stages of disease[2]. Patients with early-stage resected PAC have the best prognosis when followed by treatment with adjuvant therapy[3,4], with a median overall survival (OS) of approximately 3 years[5]. Potential predictive and prognostic biomarkers could play an important role in determining the most effective and productive treatment for individual patients. PAC is genetically heterogeneous and several well-known and some newly defined core signaling pathways likely play a role in development and behavior of PAC, including necroptosis, a form of cell death, and the DNA damage response pathway[6]. In this review, we will explore those pathways and putative biomarkers associated with them[7].

BIOMARKERS AND PAC

The Food and Drug Administration (FDA) defines a biomarker as "any measureable diagnostic indicator that is used to assess the risk or presence of disease"[8]. In recent years, there has been a tremendous increase in research directed towards identifying biomarkers in specific cancers. There are many biomarkers being used in other cancers that aid in the diagnosis and establishment of personalized treatment for patients. Though the use of biomarkers in the treatment of cancer is expanding, the role of biomarkers in the treatment of patients with PAC trails behind. To date, CA 19-9, discovered in 1981, remains as the only FDA approved biomarker in diagnosing PAC. Other cancers are also associated with elevated CA 19-9 levels including the following: Colorectal[9], esophageal[10], lung[11], ovarian[12], and breast[10], making CA 19-9 a nonspecific marker. Patients with pancreatitis, elevated bilirubin levels, and cirrhosis can also present with elevated CA 19-9 levels[13]. This makes it difficult to determine whether these levels are high due to tumor involvement or non-cancerous events. CA 19-9 is also viewed as a poor prognostic tool due to the fact that it is not expressed in 10% of Caucasians and 40% of Africans[14]. This is due to a deficiency in fucosyltransferase enzyme which is involved in the production of CA 19-9 and Lewis antigen. Currently, CA 19-9 is most useful as a diagnostic tool when measured after resection for disease recurrence[15].

Prognostic biomarkers that hold promise are SMAD4 and glypican-1 (GPC1). GPC1 is a cell surface proteoglycan located on cancer-cell-derived exosomes. Melo *et al*[16] were able to distinguish between healthy subjects and patients with a benign pancreatic disease from patients with early- and late-stage pancreatic cancer by measuring serum levels of $GPC1^+$ circulating exosomes (crExos). Levels of $GPC1^+$ crExos also were found to connect with tumor burden and the survival of pre- and post-surgical patients[16].

Mutations that inactivate SMAD Family Member 4 (SMAD4) occur most commonly in pancreatic cancers *vs* other cancer types[17]. SMAD4 is silenced in 53% of pancreatic cancer cases[18]. SMAD4 expression is lost through loss of heterozygosity and intragenetic mutations along with other alterations such as KRAS mutations[19]. KRAS mutations, located in 95% of pancreatic cancers[20], are usually followed by loss of SMAD4 in late development of PAC[21]. Loss of SMAD4 promotes the progression of preneoplastic lesions and is associated with worse prognosis in patients with PAC. Numerous studies support this claim[22-27]. Blackford *et al*[22] determined that patients whose cancers lacked SMAD4 expression had significantly worse survival outcomes than patients with normal SMAD4 expression. Tascilar *et al*[23] built on this observation by showing that the loss of expression of the SMAD4 protein by immunolabeling is associated with poor prognosis in patients with resected PAC, and patients with intact SMAD4 expression survived significantly longer than patients whose cancers lacked SMAD4 (median survival, 19.2 *vs* 14.7 mo; $P = 0.03$). Biankin *et al*[24] concluded that SMAD4 expression predicted increased survival and improved response to surgery. Reduced survival in colon cancer was associated with decreased SMAD4 expression in a study conducted by Isaksson-Mettävainio *et al*[25]. Reduced SMAD4 expression is also present in head- and - neck squamous cell carcinomas and esophageal squamous cell carcinoma[19]. SMAD4 expression is lost

in 40%-50% of colon cancers[25] and 25% of prostate cancers[26]. In 45% of cholangiocarcinomas, loss of SMAD4 expression is present and associated with more aggressive tumor behavior[27].

Identifying biomarkers

Identification and validation of predictive biomarkers for responsiveness to adjuvant therapy is extremely important for patients with PAC. These markers can be used clinically to optimize and personalize therapy for individual patients. At this point, no biomarkers have been identified to reliably predict patient outcome, and more knowledge of potential biomarkers may aid in tailoring and directing patient therapy. Our group has previously identified several potential prognostic markers involved in either the necroptotic or DDR pathway including chromodomain-helicase-DNA binding protein 5 (CHD5), CHD7, and mixed lineage kinase domain-like protein (MLKL) (Table 1).

DDR serves as cancer barrier

As defined by Curtin[28] the DDR is a series of pathways that "coordinates the repair of DNA and the activation of cell cycle checkpoints to arrest the cell to allow time for repair". The DDR has evolved in order to maintain the genomic integrity of the cell. It constantly protects the cell from endogenous and environmental damage that could disrupt DNA by causing single stranded breaks or double stranded breaks (DSBs). The DDR acts as a cancer barrier by activating DNA repair mechanisms and apoptosis so that unstable cells will not replicate and result in DDR related diseases and precancerous lesions.

One pathway of the DDR is homologous recombination repair (HRR). Occurring during the S and G_2 phases of the cell cycle[29], HRR is associated with familial forms of pancreatic cancer associated with the following genes: *BRCA1, BRCA2, PALB2, ATM, RAD51D,* and *RAD51C*[30]. HRR repairs DSBs. γH2Ax foci are markers for DSBs in precancerous lesions. These markers are produced during a phosphorylation reaction following chromatin engulfing the DSB[31,32].

Data has shown that the DDR may promote the survival of PAC that outgrows the selection pressure of DDR activation[33]. Many *DDR* genes are somatically mutated in PAC, including *ATM, BRCA2, CDKN2A, FANCI, HELB, and RAD9*[34]. Dysregulated expression of tumor suppressor genes that induce DDR activation can function as biomarkers for poor outcome.

CHD5 functions as a tumor suppressor gene

CHD5 is a member of a family of chromodomain enzymes that belong to the ATP-dependent chromatin remodeling protein superfamily. It has been suggested that CHD5 is the master regulator of a tumor-suppressive network[35]. CHD5 is regulated by DNA methylation of its promotor and histone modifications. The ability of CHD5 to bind unmodified histone 3 is essential for tumor suppression[36]. CHD5 is epigenetically silenced in neuroblastoma[37], colorectal cancer[38], breast cancer[39], cervical cancer[39], hepatocarcinoma[39], gastric cancer[40] and lung cancer[41]. Mutations in CHD5 have been found in head and neck squamous cell carcinoma[42], prostate cancer[43], ovarian cancer[44], ovarian clear cell carcinoma[45], cutaneous melanoma[46], hepatocellular carcinoma[47], neuroblastoma[48], breast and colorectal cancer[49]. In a study conducted by Bagchi *et al*[50] loss of CHD5 enhanced tumor proliferation whereas restoration of CHD5 inhibited proliferation. The function of CHD5 has mainly been studied in neural tissues where it was determined to control cell death and replication *via* the p19(Arf)/p53 pathway[50]. CHD5 is also a putative substrate of the ATM/ATR checkpoint kinases, suggesting that it may have a role in the DDR[51].

Silencing of CHD5 activates the DDR

Expression of CHD5 corresponds with a cell's capability of locating and repairing DNA damage in cells. In a study conducted by Hall *et al*[33] preclinical data showed increased levels of γH2AX foci markers suggesting increased levels of DSBs in pancreatic cancer cells. This was correlated with low CHD5 expression in those cells. As a result, activation of the DDR presumes due to the presence of collapsed replication forks[33].

Low CHD5 expression is associated with worse clinical outcomes

In the same study by Hall *et al*[33] the relationship between CHD5 levels in pancreatic cells and DDR activation was evaluated in a clinical population. The OS of 80 patients with resected PAC was analyzed in conjunction with CHD5 expression. Low CHD5 expression was associated with decreased recurrence free survival (RFS) and decreased OS in patients with PAC (5.3 *vs* 15.4 mo, $P = 0.03$)[33]. The association between low CHD5 expression and poor survival has also been documented in other cancers, including gallbladder carcinoma[52], neuroblastoma[53], ovarian cancer[54] and breast cancer[55].

CHD5 as a prognostic biomarker

Available data seems to reflect that low CHD5 expression suggests a poor prognosis. If validated in an independent cohort, low CHD5 expression could be used to select patients with particularly aggressive disease for further adjuvant therapy. Due to its clinical relevance as both a tumor suppressor and a prognostic factor in numerous cancers, study of CHD5 function in the DDR warrants further review.

CHD7 as a potential DDR substrate

CHD7 is a member of a family of chromodomain enzymes that encode an ATP-dependent chromatin remodeler. Mutations in CHD7 causes CHARGE syndrome, a multiple anomaly disorder that presents with a variety of phenotypes, including ocular coloboma, heart defects, choanal atresia, retarded growth and development, genitourinary hypoplasia, and ear abnormalities[56]. Mutations in CHD7

Table 1 Summary of chromodomain-helicase-DNA binding protein 5, 7 and mixed lineage kinase domain-like protein biomarkers in pancreatic adenocarcinoma

Biomarker	Pathway affected	Biomarker type for pancreatic cancer from literature and studies? (prognostic, predictive, diagnostic)	Mechanism of action	Other cancers	Comments
CHD5[33]	DDR	Prognostic	Tumor suppressor gene. Binds to histone 3	Epigenetically silenced in neuroblastoma[37], colorectal cancer[38], breast cancer[39], cervical cancer[39], hepatocarcinoma[39], gastric cancer[40] and lung cancer[41]. Mutations found in head and neck squamous cell carcinoma[42], prostate cancer[43], ovarian cancer[44], ovarian clear cell carcinoma[45], cutaneous melanoma[46], hepatocellular carcinoma[47], neuroblastoma[48], breast and colorectal cancer[49]	Low expression correlates with worse clinical outcomes
CHD7[66]	DDR	Prognostic	Interacts with SOX2 to regulate gene expression	-	Decreased expression is associated with improved clinical outcomes
MLKL[74]	Necroptosis	Prognostic	Forms necrosis-inducing complex called a "necrosome" along with RIPK1 and RIPK3	Ovarian[75]	Low expression is associated with worse clinical outcomes

DDR: DNA damage response pathway; SOX2: (Sex Determining Region Y)-Box 2; RIPK1: Receptor-interacting serine/threonine-protein kinase 1; RIPK3: Receptor-interacting serine/threonine-protein kinase 3.

also cause Kallman Syndrome, a genetic disorder marked by hypogonadotropic hypogonadism and anosmia[57], and associated with colorectal carcinomas[58]. CHD7 helps to regulate neural crest gene expression[59], regulates ribosomal RNA biogenesis[60], and interacts with SOX2 to regulate gene expression[61]. CHD7 is also a potential substrate of the ATM/ATR checkpoint kinases, suggesting a role in the DDR[51,62]. CHD7 is also dysregulated in 13% to 35% of cases of pancreatic adenocarcinoma, with aberrant expression, copy-number variation, and somatic mutations[63-65].

Low CHD7 expression associated with better prognosis

Colbert *et al*[66] suggested that CHD7 deficiency may play a role in gemcitabine sensitization in pancreatic adenocarcinoma cells and delayed pancreatic tumor xenograft growth in mice treated with gemcitabine. Additionally, they showed that CHD7 knockdown impaired ATR-dependent phosphorylation of CHK1 and increased gemcitabine-induced DNA damage *in vitro*, revealing a novel function for CHD7 as a DDR protein: The maintenance of genome integrity in response to gemcitabine[66]. Low CHD7 expression was also associated with improved RFS and OS in a retrospective analysis of patients with early-stage resected pancreatic adenocarcinoma treated with adjuvant gemcitabine[65].

CHD7 as a prognostic biomarker

The study conducted by Colbert *et al*[66] suggests that CHD7 expression could potentially be explored as a prognostic biomarker to personalize adjuvant therapy for these patients by determining which patients will receive greater benefit from gemcitabine therapy and allowing clinicians a way to better select patients for specific adjuvant therapy regimens in the future.

The necroptotic pathway and MLKL

Cell death is mediated through two processes, necrosis and apoptosis. Apoptosis is characterized by chromatin condensation, cell shrinkage, plasma membrane blebbing, and formation of apoptotic bodies[67]. Necrosis is characterized by oncosis, organelle swelling, and plasma membrane rupture[68]. Many cancer treatments, including chemotherapy and radiation, induce necrotic cell death[68-70]. Necrosis has been deemed a passive and unregulated process in contrast to apoptosis, however, emerging evidence has shown that necrosis can occur in a regulated and controlled manner[71]. Tumor necrosis factors (TNF)-induced necrotic death is called necroptosis[72]. Necroptosis is dependent on the activities of receptor-interacting protein kinase 1 (RIPK1) and 3 (RIPK3)[68].

Along with RIPK1 and RIPK3, MLKL forms the necrosis- inducing complex called a "necrosome"[73]. MLKL is considered a dead kinase due to its lack of phosphate-binding glycine-rich *P* loop and the absence of a key amino acid, aspartate, required for kinase activity. The necrosome induces cell death through the phosphorylation of MLKL by RIPK3 through the kinase-like domain[73]. The activity between MLKL and RIPK3 is amplified by TNF-α-mediated RIPK1 activation[73].

Low MLKL associated with worse prognosis

Colbert *et al*[74] explored MLKL expression as a potential prognostic biomarker in patients undergoing resection for

early-stage PAC. Low expression of MLKL was associated with decreased OS regardless of whether adjuvant therapy was used[74]. The HR for death associated with low MLKL expression became stronger in the group of patients treated with adjuvant therapy than in all patients, and was strongest in those patients receiving gemcitabine chemotherapy[74]. In a study conducted by He *et al*[75] low expression of MLKL was significantly associated with decreased DFS and OS in patients with primary ovarian cancer. The finding low MLKL expression is associated with worse outcomes in patients with primary ovarian cancer and early-stage PAC may be a result of decreased necroptosis signaling. This suggests that necroptosis is an important determinant of cancer cell death and outcome of patients with these cancers[75]. Study of this gene warrants further analysis as patients with low MLKL expression may benefit from more aggressive chemotherapy regimens or participation in clinical trials due to the low probability that they will benefit from traditional adjuvant therapy. Although MLKL expression may be a useful prognostic marker, further studies should be performed in other patient populations and in larger studies for validation. Also, future studies should also examine the role of MLKL in predicting response to gemcitabine therapy.

CONCLUSION

In the biomarker studies conducted for CHD5, CHD7, and MLKL, each individual gene might serve as an independent prognostic biomarker for patients with early-stage resected PAC. The findings presented provide hypothesis generating momentum to study the expression of these genes in prospective cohorts undergoing adjuvant therapy for PAC. In future studies, using larger patient cohorts, it can be determined whether multiple gene expression provides a more accurate prognostic value than single gene expression alone. The potential exists for clinicians to use biomarkers such as CHD5, CHD7, and MLKL to select the most beneficial therapy regimens and tailor them for individual patients in the future.

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