Pancreatobiliary Pathology Society Journal Watch

October November 2018

Last Update on 2018-10-05

Contents

The Current PBPath Journal Watch Articles

Wellcome to our journal watch for pancreatobiliary pathology articles, which is released every other month. You may find the previous issues in the archive.

We have created several categories for convenience; however, articles in each category are in no particular order.

Please feel free to fill out our feedback form. You may also recommend articles to be included.

Surgical Pathology

Pancreas

Rab14 overexpression regulates gemcitabine sensitivity through regulation of Bcl-2 and mitochondrial function in pancreatic cancer

Link to full abstract

Virchows Archiv : an international journal of pathology 2018 Sep;():

Rab family protein Rab14 has been implicated in the development of human cancers. To date, its expression pattern, biological function, and potential mechanism in pancreatic cancer have not been explored. In this study, we analyzed Rab14 expression in 103 cases of pancreatic cancer tissues using immunohistochemistry (IHC) and found that Rab14 was overexpressed in 41/103 cases (39.8%). Rab14 overexpression correlated with the advanced stage. Moreover, elevated Rab14 levels indicated poor prognosis of patients with pancreatic cancers. We used BxPC-3 and Capan-2 respectively for plasmid and siRNA transfection. MTT and colony formation assays showed that Rab14 transfection increased cell proliferation and colony formation in BxPC-3 cells. Rab14 siRNA knockdown inhibits proliferation and colony formation ability in Capan-2 cell line. Cell cycle analysis showed that Rab14 facilitated cell cycle progression. Matrigel invasion assay showed that Rab14 promoted BxPC-3 cell invasion while its depletion inhibited Capan-2 cell invasion. In addition, MTT and AnnexinV/PI analysis demonstrated that overexpression of Rab14 reduced gemcitabine sensitivity which conversely was increased by Rab14 knockdown. We also demonstrated that Rab14 upregulated mitochondrial membrane potential (MMP) while its depletion downregulated MMP during gemcitabine treatment. In addition, western blotting revealed that Rab14 overexpression upregulated cyclin D1, cyclin A, cyclin E, p-Rb, and Bcl-2 and downregulated p21. Rab14 also downregulated caspase3, PARP cleavage, and cytochrome c release. In conclusion, our data indicated that Rab14 was overexpressed in pancreatic cancer and promotes growth and gemcitabine resistance, possibly through regulation of mitochondrial function and Bcl-2.

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PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30267303

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PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30267303

- **CD138/syndecan-1 in pancreatic solid and pseudopapillary neoplasms**

Journal of clinical pathology 2018 Oct;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30275097

Neuroendocrine

- **The use of Ki-67 labeling index to grade pulmonary well-differentiated neuroendocrine neoplasms: current best evidence**

https://www.nature.com/articles/s41379-018-0076-9

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Cytopathology

Pancreas

- Rationale and feasibility of mucin expression profiling by qRT-PCR as diagnostic biomarkers in cytology specimens of pancreatic cancer

Pancreatology : official journal of the International Association of Pancreatology (IAP) … [et al.] 2018 Sep;():

BACKGROUND: Aberrantly expressed mucin glycoproteins (MUC) play important roles in pancreatic ductal adenocarcinoma (PDAC), yet their use as a diagnostic aid in fine-needle aspiration biopsy (FNAB) is poorly documented. The aim of this study was to investigate the rationale and feasibility of mucin (MUC1, MUC2, MUC3, MUC4, MUC5AC, and MUC6) expression profiling by RT-PCR for diagnostic applications in cytology. METHODS: Mucin expression was examined by RT-PCR and immunohistochemistry in specimens resected from patients with pancreatic (n = 101), ampullary (n = 23), and common bile duct (n = 10) cancers and 33 with chronic pancreatitis. Furthermore, mucin profiling by RT-PCR was prospectively compared in surgical and biopsy specimens of 40 patients with pancreatic solid tumours qualified for FNAB prior to surgery. RESULTS: A logistic regression model to distinguish PDAC from chronic pancreatitis using RT-PCR profiling included MUC3, MUC5AC, and MUC6. The same set of mucins differentiated ampullary and bile duct cancers from chronic pancreatitis. AUCs for the ROC curves derived from the two models were 0.95 (95%CI 0.87-0.99) and 0.92 (95%CI 0.81-0.98), respectively. The corresponding positive likelihood ratios were 6.02 and 5.97, while the negative likelihood ratios were 0.10 and 0.12. AUCs of ROC curves obtained by RT-PCR and immunohistochemistry demonstrated that both analytical methods were comparable. Surgical and cytological samples showed significantly correlated values of ΔCt for individual mucins with the overall Pearson's correlation coefficient r = 0.841 (P = 0.001). CONCLUSIONS: Mucin expression profiling of pancreatic cancer with RT-PCR is feasible and may be a valuable help in discriminating malignant lesions from chronic pancreatitis in FNAB cytology.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30268674

- **Rationale and feasibility of mucin expression profiling by qRT-PCR as diagnostic biomarkers in cytology specimens of pancreatic cancer**

https://www.sciencedirect.com/science/article/pii/S1424390318306859

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Molecular Pathology

Pancreas

- **Referral frequency, attrition rate, and outcomes of germline testing in patients with pancreatic adenocarcinoma**

https://link.springer.com/article/10.1007/s10689-018-0106-2

Ampulla of Vater

- MiR-21 up-regulation in ampullary adenocarcinoma and its pre-invasive lesions

Pathology, research and practice 2018 Jun;214(6):835-839

Poor information is available on the molecular landscape characterizing the carcinogenetic process leading to ampullary carcinoma. MiR-21 is one of the most frequently up-regulated miRNAs in pancreatic adenocarcinoma, a tumor sharing similar molecular features with ampullary adenocarcinomas (AVCs), above all with the pancreatic-biliary type. We profiled, by in situ hybridization (ISH), miR-21 expression in a series of 26 AVCs, 50 ampullary dysplastic lesions (35 low-grade [LG-IEN] and 15 high-grade [HG-IEN]) and 10 normal duodenal mucosa samples. The same series was investigated by immunohistochemistry for -catenin, p53 and HER2 expression. HER2 gene amplification was evaluated by chromogenic in situ hybridization. To validate miR-21 ISH results we performed miR-21 qRT-PCR analysis in a series of 10 AVCs and their matched normal samples. All the normal control samples showed a negative or faint miR-21 expression, whereas a significant miR-21 up-regulation was observed during the carcinogenetic cascade ($p < 0.001$), with 21/26 (80.8%) of cancer samples showing a miR-21 overexpression. In comparison to control samples, a significant overexpression was found in samples of LG-IEN ($p = .0003$), HG-IEN ($p = .0001$), and AVCs ($p < 0.0001$). No significant difference in miR-21 overexpression was observed between LG-IEN, HG-IEN and AVCs. By qRT-PCR analysis, AVCs showed a 1.7-fold increase over the controls ($p = .003$). P53 was frequently dysregulated in both dysplastic and carcinoma samples (44 out of 76; 57.9%). A 20% (10/50) of dysplastic lesions and 11% (3/26) of carcinomas were characterized by a nuclear localization of -catenin. Only 2 AVCs (7.7%; both intestinal-type) showed a HER2 overexpression (both 2+), which corresponded to a HER2 gene amplification at CISH analysis. This is the first study demonstrating a miRNA dysregulation in the whole spectrum of ampullary carcinogenesis. MiR-21 overexpression is an early molecular event during ampullary carcinogenesis and its levels increase with the neoplastic progression.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=29731265

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Others

Pancreas

- Management of pregnancy-associated pancreatic cystic tumors: Review of the literature and results of a Pancreas Club Inc. Survey

Pancreatology : official journal of the International Association of Pancreatology (IAP) ... [et al.] 2018 Sep;():

BACKGROUND/OBJECTIVES: Management of patients with pregnancy-associated cyst pancreatic cystic tumors (PA-PCT) is complicated by lack of large series. METHODS: A systematic literature review was conducted to extrapolate data on management of PA-PCT, and make a questionnaire on pending issues to be administered to the members of the Pancreas Club Inc. RESULTS: The literature review demonstrated a total of 35 PA-PCT in 34 women, described exclusively in the form of case reports, and permitted the identification of eleven key questions to be addressed in the survey. The combined analysis of literature review and survery responses provided several information. First, PA-PCT are predominantly located in the body-tail of the pancreas, cause non-specific symptoms, are of large size (mean size: 11.2 ± 4.5 cm), and are nearly always malignant or premalignant, making timing of surgery, and not indication for surgery, the main issue in the management of these tumors. Second, there is a risk of PA-PCT rupture during pregnancy. Ruptured PA-PCT had a mean size 13.5 ± 4.9 cm, but no prognostic factor could be identified. Survey opinions suggested that this occurrence is quite rare, even for large tumors. Third, most pregnancies were conducted to term (mean gestational age: 40.5 ± 0.7 weeks), with a vaginal delivery. Fourth, all procedures were carried out through an open approach and the spleen was rarely preserved. Survey indicated instead that laparoscopy could play a role, and that the spleen should be preserved when feasible. CONCLUSIONS: PA-PCT require individualized treatment. The definition of a management algorithm requires the implementation of an International Registry.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30274883

Pancreas Microenvironment

- Elucidating the link between collagen and pancreatic cancer: what's next?

Expert review of gastroenterology & hepatology 2018 04;12(4):315-317

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=29495889

Pancreas Reviews and Meta Analysis

30269131

- Precursor Lesions of Pancreatic Cancer

Oncology research and treatment 2018 ;41(10):603-610

Pancreatic ductal adenocarcinoma (PDAC) is one of the leading causes of cancer death. Although the treatment modalities are improving, the prognosis of PDAC continues to be poor. Therefore, early detection of PDAC or its precursor lesions may be the best way to improve patient survival. PDACs have several different precursor lesions, including pancreatic intraepithelial neoplasias (PanINs), intraductal papillary mucinous neoplasms (IPMNs), intraductal tubulopapillary neoplasms (ITPNs), intraductal oncocytic papillary neoplasms (IOPNs), and mucinous cystic neoplasms (MCNs). PanINs cannot be identified using imaging modalities, while the other lesions are radiologically detectable. These precursor lesions are categorized based on structural and cytological atypia as low-grade and high-grade lesions. We discuss recent updates regarding histopathological and molecular pathological overviews of PDAC precursor lesions. Better understanding of such lesions may contribute to earlier detection of PDAC or its precursor lesions and improve PDAC patient survival.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30269131

Pancreas Techniques & Research Methods

- ** A "Clearer" View of Pancreatic Pathology: A Review of Tissue Clearing and Advanced Microscopy Techniques. **

https://europepmc.org/abstract/med/30256228

Animal Studies

- Host IDO2 gene status influences tumor progression and radiotherapy response in KRAS-driven sporadic pancreatic cancers

Clinical cancer research : an official journal of the American Association for Cancer Research 2018 Sep;():

PURPOSE: Heritable genetic variations can affect the inflammatory tumor microenvironment, which can ultimately impact cancer susceptibility and clinical outcomes. Recent evidence indicates that IDO2, a positive modifier in inflammatory disease models, is frequently upregulated in pancreatic ductal adenocarcinoma (PDAC). A unique feature of IDO2in humans is the high prevalence of two inactivating single nucleotide polymorphisms (SNPs) which affords the opportunity to carry out loss-of-function studies directly in humans. In this study we sought to address whether genetic loss of IDO2 may influence PDAC development and responsiveness to treatment. EXPERIMENTAL DESIGN: Transgenic Ido2+/+and Ido2-/-micein which oncogenic KRAS is activated in pancreatic epithelial cells were evaluated for PDAC. Two patient datasets (N=200) were evaluated for the two IDO2-inactivating SNPs together with histologic, RNA expression and clinical survival data. RESULTS: PDAC development was notably decreased in the Ido2-/- mice (30% vs 10%, $P<0.05$), with a female predominance similar to the association observed for one of the human SNPs. In patients, the biallelic occurrence of either of the two IDO2-inactivating SNPs was significantly associated with markedly improved disease-free survival in response to adjuvant radiotherapy ($P<0.01$), a treatment modality that has been highly debated due to its variable efficacy. CONCLUSIONS: The results of this

study provide genetic support for IDO2 as a contributing factor in PDAC development and argue that IDO2genotype analysis has the immediate potential to influence the PDAC care decision-making process through stratification of those patients who stand to benefit from adjuvant radiotherapy.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30266763

Gallbladder

- **A case report of intracholecystic papillary neoplasm of the gallbladder resembling a submucosal tumor**

https://link.springer.com/article/10.1186/s40792-018-0524-2

- Intravascular Large B-Cell Lymphoma of the Gallbladder

Turkish journal of haematology : official journal of Turkish Society of Haematology 2018 May;35(2):145-146

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=29391332

Gallbladder Reviews and Meta Analysis

- **Outcomes of surgical resection of gallbladder cancer in patients presenting with jaundice: A systematic review and meta-analysis**

https://onlinelibrary.wiley.com/doi/abs/10.1002/jso.25186

Ampulla of Vater

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[Prognostic factors in adenocarcinoma of the ampulla of Vater].

https://www.ncbi.nlm.nih.gov/pubmed/?term=30269771

- ;():*

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=

Database SEER, NCDB, TCGA, Oncomine Studies

- **The incidence and survival of pancreatic cancer by histology, including rare subtypes: a nation-wide cancer registry-based study from Taiwan**

https://onlinelibrary.wiley.com/doi/pdf/10.1002/cam4.1795

- **Surgical resection of lymph node positive intrahepatic cholangiocarcinoma may not improve survival**

https://www.sciencedirect.com/science/article/pii/S1365182X18339352

- Global surveillance of trends in cancer survival 2000-14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries

Lancet (London, England) 2018 03;391(10125):1023-1075

BACKGROUND: In 2015, the second cycle of the CONCORD programme established global surveillance of cancer survival as a metric of the effectiveness of health systems and to inform global policy on cancer control. CONCORD-3 updates the worldwide surveillance of cancer survival to 2014. METHODS: CONCORD-3 includes individual records for 37 · 5 million patients diagnosed with cancer during the 15-year period 2000-14. Data were provided by 322 population-based cancer registries in 71 countries and territories, 47 of which provided data with 100% population coverage. The study includes 18 cancers or groups of cancers: oesophagus, stomach, colon, rectum, liver, pancreas, lung, breast (women), cervix, ovary, prostate, and melanoma of the skin in adults, and brain tumours, leukaemias, and lymphomas in both adults and children. Standardised quality control procedures were applied; errors were rectified by the registry concerned. We estimated 5-year net survival. Estimates were age-standardised with the International Cancer Survival Standard weights. FINDINGS: For most cancers, 5-year net survival remains among the highest in the world in the USA and Canada, in Australia and New Zealand, and in Finland, Iceland, Norway, and Sweden. For many cancers, Denmark is closing the survival gap with the other Nordic countries. Survival trends are generally increasing, even for some of the more lethal cancers: in some countries, survival has increased by up to 5% for cancers of the liver, pancreas, and lung. For women diagnosed during 2010-14, 5-year survival for breast cancer is now 89 · 5% in Australia and 90 · 2% in the USA, but international differences remain very wide, with levels as low as 66 · 1% in India. For gastrointestinal cancers, the highest levels of 5-year survival are seen in southeast Asia: in South Korea for cancers of the stomach (68 · 9%), colon (71 · 8%), and rectum (71 · 1%); in Japan for oesophageal cancer (36 · 0%); and in Taiwan for liver cancer (27 · 9%). By contrast, in the same world region, survival is generally lower than elsewhere for melanoma of the skin (59 · 9% in South Korea, 52 · 1% in Taiwan, and 49 · 6% in China), and for both lymphoid malignancies (52 · 5%, 50 · 5%, and 38 · 3%) and myeloid malignancies (45 · 9%, 33 · 4%, and 24 · 8%). For children diagnosed during 2010-14, 5-year survival for acute lymphoblastic leukaemia ranged from 49 · 8% in Ecuador to 95 · 2% in Finland. 5-year survival from brain tumours in children is higher than for adults but the global range is very wide (from 28 · 9% in Brazil to nearly 80% in Sweden and Denmark). INTERPRETATION: The CONCORD programme enables timely comparisons of the overall effectiveness of health systems in providing care for 18 cancers that collectively represent 75% of all cancers diagnosed worldwide every year. It contributes to the evidence base for global policy on cancer control. Since 2017, the Organisation for Economic Co-operation and Development has used findings from the CONCORD programme as the official benchmark of cancer survival, among their indicators of the quality of health care in 48 countries worldwide. Governments must recognise population-based cancer registries as key policy tools that can be used to evaluate both the impact

of cancer prevention strategies and the effectiveness of health systems for all patients diagnosed with cancer. FUNDING: American Cancer Society; Centers for Disease Control and Prevention; Swiss Re; Swiss Cancer Research foundation; Swiss Cancer League; Institut National du Cancer; La Ligue Contre le Cancer; Rossy Family Foundation; US National Cancer Institute; and the Susan G Komen Foundation.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=29395269

- **Achieving better cancer intelligence for global cancer control**

Lancet (London, England) 2018 03;391(10125):1003-1004

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=29395271

- **Pattern of distant metastases in primary extrahepatic bile-duct cancer: A SEER-based study**

Cancer medicine 2018 Sep;():

Extrahepatic bile duct cancer (EBDC) is a combined type of malignancy mainly consisting of extrahepatic cholangiocarcinoma and gallbladder cancer. Clinically, it is featured with latent symptoms and early metastasis, leading to a poor prognosis. Therefore, this cohort study aimed to depict the possible metastatic patterns of EBDC of diverse sub-types and evaluate the prognostic significance of diverse metastatic destinations with data from the clinical database. Relevant data of total 4061 confirmed EBDC patients diagnosed between 2010 and 2013 from the Surveillance, Epidemiology and End Results (SEER) database was obtained. We applied t test to describe the baseline data of patients included and used chi-square test to compare the distribution of distant metastatic sites. We further adopted odds ratio assess the combined metastatic patterns and compared survival difference of patients with different distal metastasis organ by Kaplan-Meier analysis. We identified totally 4061 patients over 18 years old diagnosed with extrahepatic bile tract malignancies between 2010 and 2013, with clear metastatic status and follow-up data, without primary malignancies. Liver and distant lymph (DL) are the two most common sites as a single metastasis organ. In combined metastasis patterns, bi-organ is more frequent than the other types. Lung is the organ preferentially for bi-organ metastasis, while bone and distant lymph similarly intend to co-metastasize with brain. Distal metastasis in EBDC patients indicates an extremely poor prognosis. According to the final analysis results, malignancies in extrahepatic bile duct exhibit similar metastatic patterns, suggesting that we can regard them as a unity to assess its development. Profound differences exist in distribution of distant extrahepatic metastatic sites and their combinations. Results from our studies would provide some information for follow-up strategies and future studies.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30277653

- **Pancreatic cancer and autoimmune diseases: An association sustained by computational and epidemiological case-control approaches: Autoimmune diseases and pancreatic cancer risk**

https://www.researchgate.net/publication/327754246_Pancreatic_cancer_and_autoimmune_diseases_An_association_sustained_by_computational_and_epidemiological_case-control_approaches_Autoimmune_diseases_and_pancreatic_cancer_risk

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Journals Reviewed

Advances in Anatomic Pathology
American Journal of Clinical Pathology
The American Journal of Gastroenterology
The American Journal of Pathology
American Journal of Surgical Pathology
Annals of Diagnostic Pathology
Annals of Surgery
Annals of Surgical Oncology
Annual Review of Pathology-Mechanisms of Disease
APMIS
Applied Immunohistochemistry & Molecular Morphology
Archives of Pathology & Laboratory Medicine
Cancer
Cancer Cell
Cancer Cytopathology
Cell
Cellular Oncology
Clinical Cancer Research
Cochrane Database Systematic Reviews
Cytojournal
Cytopathology
Diagnostic Cytopathology
Diagnostic Pathology
Endocrine Pathology
Experimental and Molecular Pathology
Expert Review of Molecular Diagnostics
Gastroenterology
Gut
Histology and Histopathology
Histopathology
Human Pathology
International Journal of Surgical Pathology
International Journal of Clinical and Experimental Pathology
Journal of Clinical Pathology
Journal of Molecular Diagnostics
Journal of Pathology
Laboratory investigation
Lancet
Medical Molecular Morphology
Modern Pathology
Nature
Nature Reviews Gastroenterology & Hepatology
NEJM
Pancreas
Pancreatology
Pathobiology
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