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Levels of Cytokines in Serum Associate With Development of Hepatocellular Carcinoma in WWW Patients With HCV Infection Treated With Direct-Acting Antivirals

J. D. Debes, M. van Tilborg, Z. M. A. Groothuismink, B. E. Hansen, J. Schulze zur Wiesch, J. von Felden, R. J. de Knegt,

The authors found a signature of immune markers in serum of patients, that predicts liver cancer development after treatment of hepatitis C virus.

Full Reports

Clinical—Alimentary Tract

518 Incidence and Treatment of Patients Diagnosed With Inflammatory Bowel Diseases at (WWW) 60 Years or Older in Sweden

Å. H. Everhov, J. Halfvarson, P. Myrelid, M. C. Sachs, C. Nordenvall, J. Söderling, A. Ekbom, M. Neovius, J. F. Ludvigsson, J. Askling, and O. Olén

Elderly onset IBD in Sweden was associated with a lower use of biologics and immunmodulators and a higher absolute risk of bowel surgery compared to younger patients.

529 Fructan, Rather Than Gluten, Induces Symptoms in Patients With Self-Reported Non-Celiac Gluten Sensitivity

G. I. Skodje, V. K. Sarna, I. H. Minelle, K. L. Rolfsen, J. G. Muir, P. R. Gibson, M. B. Veierød, C. Henriksen, and K. E. A. Lundin

See editorial on page 471.

In this randomized, double-blind, placebo-controlled crossover study of individuals with self-reported non-celiac gluten sensitivity, the authors found fructans to induce symptoms, measured by the gastrointestinal symptom rating scale irritable bowel syndrome version.

540 Low Rates of Gastrointestinal and Non-Gastrointestinal Complications for Screening or Surveillance Colonoscopies in a Population-Based Study

L. Wang, A. Mannalithara, G. Singh, and U. Ladabaum

See editorial on page 473.

The risks of heart attack, stroke and other non-GI complications after screening colonoscopy are similar to those after other minimally invasive procedures; thus, they may not significantly exceed the baseline risks in the general population.

556 Cost Effectiveness of Screening Individuals With Cystic Fibrosis for Colorectal Cancer Www A. Gini, A. G. Zauber, D. R. Cenin, A.-H. Omidvari, S. E. Hempstead, A. K. Fink, A. B. Lowenfels, and I. Lansdorp-Vogelaar

This study provides important guidance to clinicians, researchers, and policy makers who aim to define a tailored colorectal cancer screening for patients with Cystic Fibrosis. This analysis shows that screening in these individuals is cost-effective.

568 Accurate Classification of Diminutive Colorectal Polyps Using Computer-Aided Analysis P.-J. Chen, M.-C. Lin, M.-J. Lai, J.-C. Lin, H. H.-S. Lu, and V. S. Tseng

Computer-aided analysis with a deep neural network can accurately classify magnifying narrow-band images of diminutive colorectal polyps as neoplastic or hyperplastic, and is not inferior to the human eyes of experts.

Clinical—Pancreas

576 Progression of Pancreatic Branch Duct Intraductal Papillary Mucinous Neoplasm Associates E With Cyst Size

Y. Han, H. Lee, J. S. Kang, J. R. Kim, H. S. Kim, J. M. Lee, K.-B. Lee, W. Kwon, S.-W. Kim, and J.-Y. Jang

See editorial on page 475.

The authors document the natural history of BD-IPMN through long-term surveillance and suggest that the surveillance interval must be optimized according to the initial tumor size and growth rate.

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DNA Methylation and Transcription Patterns in Intestinal Epithelial Cells From Pediatric Patients With Inflammatory Bowel Diseases Differentiate Disease Subtypes and Associate With Outcome

K. J. Howell, J. Kraiczy, K. M. Nayak, M. Gasparetto, A. Ross, C. Lee, T. N. Mak, B.-K. Koo, N. Kumar, T. Lawley, A. Sinha, P. Rosenstiel, R. Heuschkel, O. Stegle, and M. Zilbauer

Impaired function of the intestinal epithelium has been implicated in pathogenesis of IBD. Epigenetic and transcriptional profiling of primary human intestinal epithelium revealed distinct disease specific alterations in children newly diagnosed with IBD which correlate with disease outcome.

Long Noncoding RNA *uc.173* Promotes Renewal of the Intestinal Mucosa by Inducing Degradation of MicroRNA 195

L. Xiao, J. Wu, J.-Y. Wang, H. K. Chung, S. Kalakonda, J. N. Rao, M. Gorospe, and J.-Y. Wang

Findings obtained from in vitro, ex vivo, and in vivo systems indicate that long noncoding RNA uc.173 stimulates regeneration of the intestinal mucosa by reducing microRNA 195 levels.

612 Genome and Methylome Variation in *Helicobacter pylori* With a *cag* Pathogenicity Island During Early Stages of Human Infection

S. Nell, I. Estibariz, J. Krebes, B. Bunk, D. Y. Graham, J. Overmann, Y. Song, C. Spröer, I. Yang, T. Wex, J. Korlach, P. Malfertheiner, and S. Suerbaum

The authors analyzed the genome sequences of *Helicobacter pylori* bacteria that had evolved in the stomachs of human volunteers and found that the large amount of genetic variation in *H pylori* poses an important challenge to vaccine development.

624 Transcription and Signaling Regulators in Developing Neuronal Subtypes of Mouse and Human Enteric Nervous System

F. Memic, V. Knoflach, K. Morarach, R. Sadler, C. Laranjeira, J. Hjerling-Leffler, E. Sundström, V. Pachnis, and U. Marklund

See editorial on page 478.

This study identifies and describes expression of genes with plausible regulatory roles in the generation of different types of enteric neurons in mouse and human embryonic gut.

637 MicroRNAs 15A and 16-1 Activate Signaling Pathways That Mediate Chemotaxis of Immune Regulatory B cells to Colorectal Tumors

R. Liu, Z. Lu, J. Gu, J. Liu, E. Huang, X. Liu, L. Wang, J. Yang, Y. Deng, J. Qian, F. Luo, Z. Wang, H. Zhang, X. Jiang, D. Zhang, J. Qian, G. Liu, H. Zhu, Y. Qian, Z. Liu, and Y. Chu

The authors found increased levels of MIR15A and MIR16-1 to reduce numbers of IgA+B cells in colorectal tumor tissues and correlate with increased survival time of patients.

Basic and Translational—Liver

652 Efficacy of NVR 3-778, Alone and In Combination With Pegylated Interferon, vs Entecavir In uPA/SCID Mice With Humanized Livers and HBV Infection

K. Klumpp, T. Shimada, L. Allweiss, T. Volz, M. Lütgehetmann, G. Hartman, O. A. Flores, A. M. Lam, and M. Dandri

See editorial on page 481.

A capsid assembly modulator (CAM) can potently block the production of HBV replication products in a mouse model with HBV infected humanized liver. CAM and interferon in combination show higher antiviral activity than previously observed with other antiviral treatments in this model.

Pan-Genotype Hepatitis E Virus Replication in Stem Cell-Derived Hepatocellular Systems X. Wu, V. L. Dao Thi, P. Liu, C. N. Takacs, K. Xiang, L. Andrus, J. Gouttenoire, D. Moradpour, and C. M. Rice

Stem cell-derived hepatocyte-like cells are permissive for pan-genotype hepatitis E virus (HEV) infection. These results reinforce the importance of using more physiologically relevant culture systems for HEV studies.

Basic and Translational—Pancreas

Interleukin 35 Expression Correlates With Microvessel Density in Pancreatic Ductal
Adenocarcinoma, Recruits Monocytes, and Promotes Growth and Angiogenesis of Xenograft
Tumors in Mice

C. Huang, Z. Li, N. Li, Y. Li, A. Chang, T. Zhao, X. Wang, H. Wang, S. Gao, S. Yang, J. Hao, and H. Ren Tumor-derived IL-35 promotes angiogenesis via recruiting and reprogramming monocytes in pancreatic ductal adenocarcinoma.

689 Mitochondrial Dysfunction, Through Impaired Autophagy, Leads to Endoplasmic Reticulum Stress, Deregulated Lipid Metabolism, and Pancreatitis in Animal Models

G. Biczo, E. T. Vegh, N. Shalbueva, O. A. Mareninova, J. Elperin, E. Lotshaw, S. Gretler, A. Lugea, S. R. Malla, D. Dawson, P. Ruchala, J. Whitelegge, S. W. French, L. Wen, S. Z. Husain, F. S. Gorelick, P. Hegyi, Z. Rakonczay Jr, I. Gukovsky, and A. S. Gukovskaya

Mitochondrial dysfunction and impaired autophagy are prominent in acinar cells during pancreatitis. Normalizing these pathways alleviates disease severity in mouse models.

704 Cathepsin B-Mediated Activation of Trypsinogen in Endocytosing Macrophages Increases

Severity of Pancreatitis in Mice

M. Sendler, F.-U. Weiss, J. Golchert, G. Homuth, C. van den Brandt, U. M. Mahajan, L.-I. Partecke, P. Döring, I. Gukovsky, A. S. Gukovskaya, P. R. Wagh, M. M. Lerch, and J. Mayerle

See editorial on page 482.

In pancreatitis, white blood cells eat (engulf) and activate digestive enzymes which fuels the systemic inflammatory process determining severity of the disease. This process could be used for disease specific therapy.

719 Exome-Wide Association Study of Pancreatic Cancer Risk

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R. C. Grant, R. E. Denroche, A. Borgida, C. Virtanen, N. Cook, A. L. Smith, A. A. Connor, J. M. Wilson, G. Peterson, N. J. Roberts, A. P. Klein, S. M. Grimmond, A. Biankin, S. Cleary, M. Moore, M. Lemire, G. Zogopoulos, L. Stein, and S. Gallinger

A case-control study of genetic variation in pancreatic cancer confirms the *BRCA2* gene as important and identifies new candidate genes for pancreatic cancer risk.

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