

Journal Scan:

Expressions of Matrix Metalloproteinases (MMP-2, MMP-7, and MMP-9) and Their Inhibitors (TIMP-1, TIMP-2) in Inflammatory Bowel Diseases

Crohn's disease (CD) and ulcerative colitis (UC) belong to a group of inflammatory bowel diseases (IBD). The authors aimed to evaluate the expression of MMP-2, MMP-7, MMP-9, TIMP-1, and TIMP-2 in 34 patients with UC and 10 patients with CD. Evaluation of MMP-2, MMP-7, MMP-9, TIMP-1, and TIMP-2 expression in tissue samples was performed using immune histochemistry. The overexpression of MMP-9 and TIMP-1 was dominant in both the glandular epithelium and inflammatory infiltration in UC patients. In contrast, in CD subjects the positive expression of MMP-2 and TIMP-1 was in glandular tubes while mainly MMP-7 and TIMP-2 expression was in inflammatory infiltration. Metalloproteinases' expression was associated with the presence of erosions, architectural tissue changes, and inflammatory infiltration in the lamina propria of UC patients. The expression of metalloproteinase inhibitors correlated with the presence of eosinophils and neutrophils in UC and granulomas in CD patients. The findings of this study indicate that the overexpression of metalloproteinases and weaker expression of their inhibitors may determine the development of IBD. It appears that MMP-2, MMP-7, and MMP-9 may be a potential therapeutic target and the use of their inhibitors may significantly reduce UC progression.

Comment

Inflammatory bowel diseases (IBD) such as Crohn's disease (CD) and ulcerative colitis (UC) are mediated by metalloproteinase, cytokines, and growth factors, and a number of cells including leukocytes and stromal cells. In the present study authors evaluated expression of MMP-2, MMP-7, MMP-9, TIMP-1, and TIMP-2 in patients with UC and CD through immunohistochemical studies. The analysis revealed that the overexpression of metalloproteinases and weaker activation of TIMPs determine the development of IBD. The study paves the way to develop potent therapeutics against inflammatory bowel diseases by designing inhibitors for MMP-7, MMP-2 and MMP-9.

Jakubowska K, Pryczynicz A, Iwanowicz P, Niewiński A, Maciorkowska E, Hapanowicz J, Jagodzińska D, Kemon A, Guzińska-Ustymowicz K. Expressions of Matrix Metalloproteinases (MMP-2, MMP-7, and MMP-9) and Their Inhibitors (TIMP-1, TIMP-2) in Inflammatory Bowel Diseases. Gastroenterol Res Pract 2016;2016:2456179.

Structure Activity Relationship for the 4(3H)-Quinazolinone Antibacterials

The authors recently reported the discovery of a novel antibacterial (2) with a 4(3H)-quinazolinone core. This discovery was made by in silico screening of 1.2 million compounds for binding to a penicillin-binding protein and the subsequent demonstration of antibacterial activity against *Staphylococcus aureus*. The first structure-activity relationship for this antibacterial scaffold was explored in this report with evaluation of 77 variants of the structural class. Eleven promising compounds were further evaluated for in vitro toxicity, pharmacokinetics, and efficacy in a mouse peritonitis model of infection, which led to the discovery of compound 27. The derivatives presented MIC of 0.03 µg/mL against ESKAPE panel with favorable pharmacodynamics properties. This new quinazolinone has potent activity against methicillin-resistant (MRSA) strains, low clearance, oral bioavailability and shows efficacy in a mouse neutropenic thigh infection model.



Online access

http://svimstpt.ap.nic.in/jcsr/jul-sep16_files/js16.pdf

Comment

Infectious diseases are the second leading cause of death and majority of the bacterial infections are due to the ESKAPE panel (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacteriaceae* species). Among the ESKAPE panel, methicillin-resistant *S. aureus* (MRSA) alone accounts for nearly half of the deaths attributed to antibiotic-resistant infections. In the present study authors targeted PBP and performed Structure-Activity Relationship of 4(3H) quinazolinone by introducing variations on rings 1, 2, and 3. As the proposed lead is a small molecule and non- β -lactam antibacterial it holds great promise in controlling infections caused by multi drug resistant ESKAPE panel.

Bouley R, Ding D, Peng Z, Bastian M, Lastochkin E, Song W, Suckow MA, Schroeder VA, Wolter WR, Mobashery S, Chang M. Structure-Activity Relationship for the 4(3H)-Quinazolinone Antibacterials. *J Med Chem* 2016;59:5011-21.

Novel personalized pathway-based metabolomics models reveal key metabolic pathways for breast cancer diagnosis

Breast cancer is the most common malignancy worldwide and hence accurate diagnostic methods are pressing needed to diagnose breast cancer. Blood-based metabolomics is a promising diagnostic method for breast cancer. The authors proposed that higher-order functional representation of metabolomics data, such as pathway-based metabolomic features, can be used as robust biomarkers for breast cancer. For this, the authors developed a new computational method that uses personalized pathway dysregulation scores for disease diagnosis.

They applied this method to predict breast cancer occurrence, in combination with correlation feature selection (CFS) and classification methods.

The resulting all-stage and early-stage diagnosis models were found to be highly accurate in two sets of testing blood samples, with average AUCs (Area Under the Curve, a receiver operating characteristic curve) of 0.968 and 0.934, sensitivities of 0.946 and 0.954, and specificities of 0.934 and 0.918. These two metabolomics-based pathway models were further validated by RNA-Seq-based TCGA (The Cancer Genome Atlas) breast cancer data, with AUCs of 0.995 and 0.993. Important metabolic pathways, such as taurine and hypotaurine metabolism and the alanine, aspartate, and glutamate pathway were found to critical biological pathways for early diagnosis of breast cancer.

Comment

Early diagnosis of breast cancer is essential as breast cancer is ranked second for deaths among cancer patients. In the present work authors developed a novel computational pathway-based model integrating metabolite features and pathway features. They identified taurine and hypotaurine metabolism and alanine, aspartate, and glutamate pathways as early stage breast cancer biomarkers. Application of the model to other omics data types could be useful for disease diagnosis, therapeutic interventions and also precision medicine.

Huang S, Chong N, Lewis NE, Jia W, Xie G, Garmire LX. Novel personalized pathway-based metabolomics models reveal key metabolic pathways for breast cancer diagnosis. *Genome Med* 2016;8:34.

Reviewers

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