Emerging molecular targets

Cystic fibrosis and airway mucin expression

Lung disease is the primary life-threatening complication of cystic fibrosis (CF). Individuals with this most common genetic disease suffer from airway obstruction by excess mucus, a decreased hydration and altered electrolyte composition of airway secretions, an unusual profile of bacterial infections, and chronic airway inflammation. Together, these aberrations promote a complex downward spiral of ever more serious successions of infection and inflammation of the airways. Today, more than 95% of the deaths attributed to CF are due to chronic lung disease.

The cause of the excessive mucus secretion in CF has long been sought. Now, Dr Jian-Dong Li and coworkers at the University of California (San Francisco, CA, USA) and Columbia University (New York, NY, USA) have found that the culture supernatant of *Pseudomonas aeruginosa*, a common organism infecting the lungs of CF patients, contains substances that trigger transcription of the mucin gene *MUC2* [*Proc. Natl. Acad. Sci. U. S. A.* (1997) 94, 967–972].

CF is caused by a host of different mutations in the gene that encodes a protein called the cystic fibrosis transmembrane conductance regulator (CFTR). This protein is normally found on the apical surface of epithelial cells, where it functions as a chloride ion channel. In CF, mutations of the CFTR gene cause the protein to either fail to be inserted into the membrane of the epithelial cell or, if it is inserted into the apical membrane, to be defective in transporting chloride ions. In the airways, the decreased hydration and the altered ionic properties of the airway secretions that arise as a consequence of the defective CFTR are believed to promote infection by *P. aeruginosa*. The findings of Li and coworkers now suggest that excess mucin production is a tertiary effect of the CFTR gene mutation that occurs as a direct result of colonization by *P. aeruginosa*.

Li and colleagues conclude that the substances in the culture supernatant responsible for activation of the *MUC2* gene are bacterial polysaccharides such as lipolysaccaride (LPS), which are common mediators of inflammation derived from Gram-negative bacteria. Their conclusion is based upon an examination of the chemical and physical properties of the activating agents in the culture medium, and the observation that purified LPS from *P. aeruginosa* was capable of activating the *MUC2* gene in a manner similar to that observed in the culture supernatants. They also report that two tyrosine kinase inhibitors, tyrophostin AG126 and genistein, block the activation of the *MUC2* gene by the components of the culture supernatant.

Future work on the details of LPS signaling leading to the activation of the *MUC2* gene in epithelial cells is likely to yield novel targets for the discovery of drugs to block the excess mucin secretion characteristic of CF. Such drugs could be highly useful in reversing the extremely complex path of lung disease that so often ends the life of the CF patient.

A membrane-bound chemokine with a CX_3 motif

Protein chemokines control the migration of T cells, monocytes, neutrophils and other cellular components of the immune system. The repertoire of proteins that make up the chemokine system is complex, and new components are still being discovered. Until now, all the known chemokines were relatively small proteins that fell into one of three structural categories based upon specific cysteine-rich motifs: CXC, CC and C, where C is a cysteine and X is any amino acid. Now, Dr J. Fernando-Bazan and coworkers at the DNAX Research Institute (Palo Alto, CA, USA) and the University of Oxford (UK) have identified a new chemokine with unusual characteristics including a distinct signature motif of CXXXC [*Nature* (1997) 385, 640–644].

The new chemokine was discovered by searching databases of DNA sequences for those genes that encode proteins with structures similar to known chemokines. Using this approach, the authors of the study found a most unusual DNA sequence that codes for a 397-amino-acid protein, of which only a portion, the 76-amino-acid N-terminus of the mature protein, contains a chemokine-like structure. The remainder of the molecule is more analogous to a mucin structure with an uninterrupted stretch of 18 hydrophobic amino acids, the hallmark of a transmembrane domain, close to the C-terminus. The newly discovered protein appears to consist of a chemokine that is dangled into the extracellular milieu at the end of a long mucin-like stalk that is anchored to the plasma membrane.

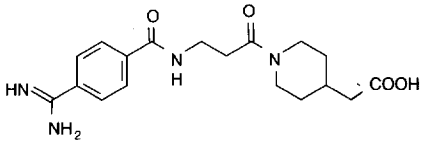
Biological studies of the newly discovered protein show that it is found on the plasma membrane of endothelial cells, where it promotes the adhesion of leukocytes. The N-terminus CXXXC chemokine portion of the molecule may be shed, and the soluble form of the chemokine acts as a chemoattractant for T cells and monocytes. A detailed search for cell-surface receptors for the soluble chemokine and an understanding of the presumed signaling activity of the membrane-bound form of the protein are likely to lead to interesting new molecular targets for the discovery of drugs to modulate immune function.

Robert W. Wallace
tel/fax: +1 212 254 3322
e-mail: RobWallace@Delphi.Com

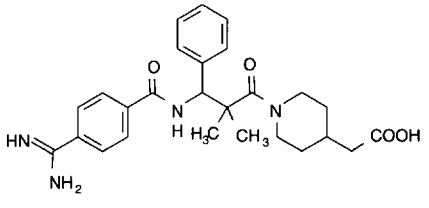
Combinatorial chemistry

A library of GPIIb/IIIa antagonists

Nonpeptide antagonists of the platelet fibrinogen receptor (GPIIb/IIIa) are useful inhibitors of platelet aggregation. Consequently they are a focus of much current medicinal chemistry research. Earlier this year, I highlighted the use of combinatorial chemistry in the optimization of an active GPIIb/IIIa antagonist [Hoekstra, W.J. *et al. Bioorg. Med. Chem. Lett.* (1996) 6, 2371–2376]. Harada, T. and coworkers [*Bioorg. Med. Chem. Lett.* (1997) 7, 209–212] have now published their own



1



2