news

Plethora of gut bugs promises personalization of drugs

Laura Nelson, lauranels@yahoo.co.uk

Sixty-two percent of the bacteria in our gut were unknown up to now, reveals a study of the colons of three people. This could lead to personalized medicine based on a particular gut microbe profile, which affects how drugs are metabolized.

Gut bacterial cells outnumber our own cells by nearly 10:1. Jeremy Nicholson, biomedical scientist at Imperial College in London, UK, says that now scientists have the genetic tools to study gut microbes, they are learning how important the bugs are in how drugs work.

Researchers at Stanford School of Medicine in California, USA, led by Paul Eckburg, studied samples taken from six regions of the inner lining of the colon or from the faeces. They identified bacteria using a gene sequence common to all bacteria. Of 13 thousand sequences, they found nearly 400 distinct types, which correspond to species [1].

Almost two thirds of the species had never been characterized

The three people differed widely in the diversity of species and in the number of species, probably due to their diet, genetics, previous illnesses, where the people lived and their ages. 'This is the first step in really characterizing what's there', says Eckburg.

Nicholson's group has started to compile similar information in rats and mice. He has found that gut bacteria content varies so much between species, and even the groups of the same species in different laboratories, that he believes this information needs to be taken into account in drug discovery.

Microbes influence metabolism in the gut [2]. Personalizing drugs should take account of different microbe populations, as well as a person's genome. 'Pharmacogenetics is not enough', Nicholson says. Also, the species of gut bacteria seem to be changing over time, partly due to the use of antibiotics, he says.

Bugs produce their own chemicals, often for defence purposes, which influence metabolism by causing induction of enzymes, for example. But they differ in their capabilities. 'Not all drugs induce enzymes equally well,' says Nicholson. The variation in the spectrum of gut bacteria affects bioavailability and also toxicity of drugs. 'In some cases drugs are made more toxic, in other cases less toxic by varying the gut microbes', says Nicholson.

'Pharmacogenetics is not enough'

Matching metabolic activity

Nicholson's group is trying to determine the metabolic action of different bugs by matching metabolic activity, by measuring metabolites in urine, with the bug profile in the guts of rats and mice. He has also looked at rats that have no gut microbes – gnotobiotic animals – and found they have a completely different pattern of enzyme induction.

With the knowledge of how drugs are metabolized according to different bug populations, drugs can be developed to suit

an individual person, and toxicity can be avoided. 'We will understand why some drugs might be more toxic in some people than others', says Nicholson. It could also lead to hybrid therapies that involve probiotics, which, by altering metabolism, could increase the effectiveness of drugs.

References

1 Eckburg, P.B. *et al.* (2005) Diversity of the human intestinal microbial flora. *Science* DOI:10.1126/science.1110591 (Epubn ahead of print; http://www.sciencemag.org)

2 Nicholson, J.K. *et al.* (2005) Gut microorganisms, mammalian metabolism and personalized healthcare. *Nat. Reviews Microbiol.* DOI:10.1038/nrmicro1152 (Epubn ahead of print; http://www.nature.com/nrmicro)

Chemokine programming of T cell responses could offer new drug targets

Kathryn Senior, kathsenior@onetel.com

A recent study has revealed that the chemokines CCL19 and CCL21 are physiologically important as potent inducers of T cell proliferation. The chemotactic activity of both molecules had been previously established as they had been shown to induce migration of T cells and dendritic cells as well as endocytosis, dendritic extension and inhibition of apoptosis. This new information increases our knowledge of the two molecules and has important implications for rational viral vaccine design and anti-cancer therapy.

Inducing Th1 response

'We show that CCL19 and CCL21, chemokines that attract dendritic cells from the periphery to T cell regions of lymphoid organs, provide a strong maturation signal for dendritic cells and the subsequent induction of a Th1 response', says senior author Martin Bachmann (Cytos Biotechnology AG, Zurich, Switzerland). 'These findings demonstrate that CCL19 and CCL21 are much more powerful pro-inflammatory proteins than previously appreciated. Blocking these molecules therefore has potential for the treatment of a variety of diseases, including rheumatoid arthritis, Crohn`s disease and perhaps even multiple sclerosis', he adds.

1359-6446/05/$ – see front matter PII: S1359-6446(05)03519-1

news

There are about 40 known chemokines in humans but most have not been thoroughly investigated. 'Most cancer studies have been done on CXCR4 as receptor but the best examples of using chemokines as drug targets are from HIV research, not cancer,' points out Ghislain Opdenakker (Rega Institute for Medical Research, University of Leuven, Belgium). Opdenakker and colleague Jo Van Damme, a noted world expert on chemokines, wrote an extensive review on the biology of chemokines and their drug development potential last year [1].

Chemokines in trial for HIV

HIV uses CCR5 and CXCR4 as coreceptors and small-sized drugs that block these receptors have been developed for HIV therapy. Dominque Schols, also of the Rega Institute in Belgium mentions that Pfizer and GSK currently have ongoing clinical trials of CCR5 inhibitors for HIV. 'For CXCR4 inhibitors, there are two different compounds in clinical studies: AMD3100 was used successfully in clinical studies for HIV, but had oral availability problems, so a follow up compound, AMD11070 is now being used,' he explains. AMD3100 is a CXCR4 inhibitor that is used now as stem cell mobilizing agent. 'This will be an important application and this effect is not seen with CCR5 inhibitors,' says Schols.

> 'CXCR4 inhibitors are likely to be useful in certain types of cancer, arthritis and asthma'

Future drug development potential

Schols believes that, generally, the potential clinical application of CXCR4 inhibitors is much broader than for a CCR5 inhibitor. AMD3100, also inhibited autoimmune joint inflammation and also attenuates allergic lung inflammation and airway hyperreactivity in several mouse models 'CXCR4 inhibitors are likely to be useful in certain types of cancer, arthritis and asthma', he predicts.

Once more drug molecules have been identified through HIV research, further experimental studies and maybe also clinical trials can begin in cancer research. 'The blocking activity of these drugs (e.g. of CXCR4 in HIV) can in the future be exploited to antagonize CXCR4 in cases where this receptor is used in invasion of cancer cells,' says Opdenakker. However, he warns that because of the multitude of chemokines, 'it is difficult for everyone, including drug companies, to define which chemokine or receptor to target.'

Reference

1 Opdenakker, G. and van Damme, J. (2004) The countercurrent principle in invasion and metastasis of cancer cells. Recent insights on the roles of chemokines. *Int. J. Dev. Biol.* 48, 519–527

1359-6446/05/$ – see front matter PII: S1359-6446(05)03517-8