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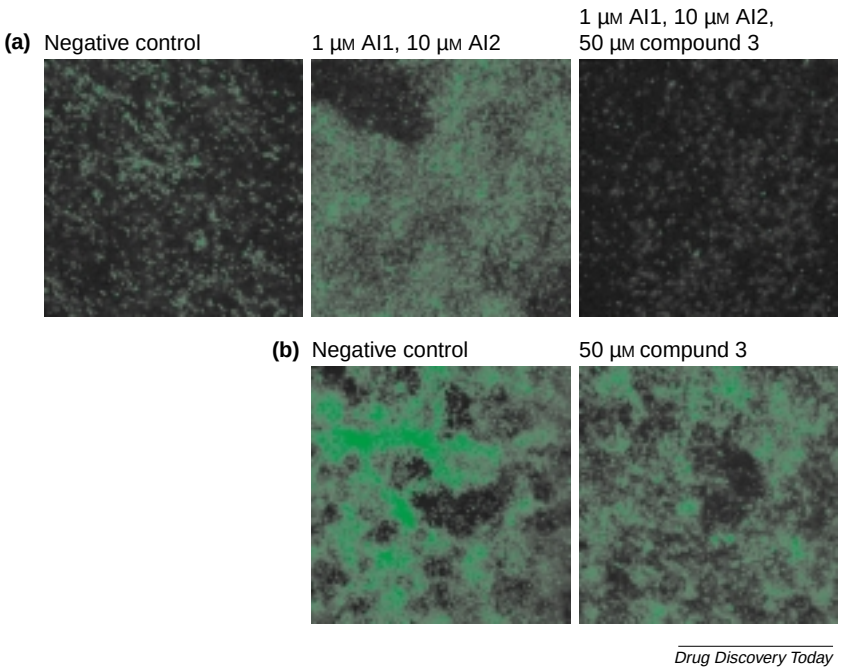

Figure 1. Effect of compounds on biofilm formation of *Pseudomonas aeruginosa*; the bacteria, which express the green fluorescent protein, are grown on cover slips in a static culture. When grown in the presence of autoinducers, the bacteria form a biofilm. The addition of compound 3 blocks biofilm formation. **(a)** *P. aeruginosa* PAO-JP2 (laboratory strain). **(b)** *P. aeruginosa* PAO-1 (wildtype strain). Figure reproduced, with permission, from Ref. [1].

of an antagonist assay support this hypothesis. Other assays revealed that compound 3 blocks the production of various virulence factors and prevents biofilm formation (Fig. 1).

Greenberg believes the result is promising. However, he is concerned that this compound itself might not be useful as a drug: 'It is too weak an inhibitor'. Indeed, compound 3 inhibited *lasI* induction by only 35%. 'But it may be possible to further develop it into a drug,' reckons Greenberg.

According to Suga, this won't be too difficult. 'The approach we used is very flexible, and it is possible to expand it by working with other focused libraries. Therefore, we can look for more potent antagonists in the future.'

Reference

1 Smith, K.M. *et al.* (2003) Induction and inhibition of *Pseudomonas aeruginosa* quorum sensing by synthetic autoinducer analogs. *Chem. Biol.* 10, 81–89

Centenarians provide genetic clue to age-related disease

Sabine Louët, freelance writer

Studies on people who have passed their 100th birthday are revealing the role of genetics in age-related disease. Many age-related diseases result from inflammatory processes, and centenarians enjoy unusually low inflammatory profiles, says Italian immunologist, Claudio Franceschi, Professor of Immunology at the University of Bologna, Italy (http://www.unibo.it).

Link between inflammation and ageing

Franceschi, says that his work on centenarians has revealed a genetic link between a mechanism for chronic inflammation and ageing. 'People are prone to develop inflammation on a genetic basis.'

Franceschi discovered that centenarians present low levels of the pro-inflammatory cytokine interleukin 6 (IL-6) and high levels of the anti-inflammatory cytokine IL-10. High levels of IL-6, which is produced in muscles and bones, is related to loss of muscle mass and power with age. Such status translates into frailty and disability and the occurrence of diseases, such as osteoporosis.

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'There is a balance between pro- and anti-inflammatory compounds [that is] genetically controlled,' Franceschi told delegates at last month's *Biochemical Society* meeting held at Imperial College in London (see http://www.biochemistry.org; http://www.ic.ac.uk). People with certain genes that trigger an imbalance between a pro- and an anti-inflammatory cytokine are more likely to suffer from chronic inflammation related to ageing, he said.

Although 25–30% of longevity is the result of a genetic background, says Efstathios Gonos, Director of Research Specialized in Ageing at the National Hellenic Research Foundation in Athens (http://www.eie.gr), 'It is extremely unlikely that there is a single gene causing longevity.'

The genetic make up of centenarians can thus provide a useful tool in the investigation of age-related diseases. Indeed, Franceschi brands centenarians 'extreme phenotypes' that comprise all the genetic elements that are necessary to avoid age-related diseases. Conversely, high IL-6 levels can be considered as a genetic marker for morbidity and mortality in the elderly.

Functionality of IL-6

This does not come as a surprise to researcher of age-related diseases Jonathan Powell, from Unilever Research in the UK (http://www.unilever.com). Pro-inflammatory cytokine IL-6 is not only linked to the immune system but is also a major metabolic regulator found in primitive organisms, such as tubeworms and starfish, which have no immune system. 'IL-6 has acquired some other functionality as we have evolved. But those old metabolic functions are still there in us,' said Powell.

'As more and more and more of these associations are found, we'll have a better idea of the predictive value of those genotypes,' he said. Genetic markers could then, one day, help to identify subjects at higher risk, and could aid in the development of a new preventative medicine. 'Inflammation does not describe all of ageing but it has a significant component, ' said Powell.

'Major age-related diseases all share an inflammatory pathogenesis,' said Franceschi. Different diseases, such as arthritis and Alzheimer's disease, share the same inflammatory mechanism, he adds. People treated with anti-inflammatory compounds for arthritis have a lower risk of getting Alzheimer's disease.

The finding of a genetic susceptibility to age-related disease also fits with an evolutionary perspective. Centenarians present low levels of pro-inflammatory cytokine IL-6, which protects them from age-related inflammatory diseases. According to Franceschi, showing a strong inflammatory response is an advantage before the age of 50 but it is detrimental in later life when the reproduction-driven force of evolution decreases. 'From an evolutionary perspective, the objective is not to live long but to be fit enough to reproduce', agreed Gonos.

In addition, Franceschi has identified a difference in cytokine levels between men and women. He believes that genetics has a greater role in protecting men from inflammatory disease than protecting women, because women have more protective hormones. 'Women are less prone to having high inflammatory status because it is detrimental for bearing children,' he said.

Improving drug response with pharmacogenomics

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Adverse drug reactions, which in the USA are estimated to account for 100,000 hospitalizations annually at a cost of US$15 billion, could be halved by the implementation of personalized medicine, says David Gurwitz of the Sackler Faculty of Medicine at Tel-Aviv University in Israel (http://www.tau.ac.il/medicine/). However, Gurwitz claims that this can only be achieved by updating medical school curricula [1].

Pharmacogenomics – the study of how genes affect drug action – promises a brave new medical world in which a quick genetic analysis reveals a patient's response to a drug, enabling treatment to be personalized and drug efficacy to be optimized. Although this vision could still be decades away, pharmacogenomics must be incorporated into medical teaching now, says Gurwitz.

A new curriculum

'The need to incorporate the teaching of pharmacogenomics into the medical curriculum is quite urgent,' said Gurwitz, who this academic year has

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