healthy brain at the molecular level, it should be possible to develop drugs that are more specific in their action and perhaps less toxic,' predicts Yolken.

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Kathryn Senior

Complement activation in myocardial infarction: a target for future treatments?

The discovery that complement activation plays a key role in triggering endothelial cell damage during myocardial infarction could lead to the development of new drugs for treating heart disease. Researchers in the US have also shown that monoclonal antibodies (mAbs) can inhibit the relevant complement activation pathway, known as the lectin complement pathway.

Leonard Bell, President and CEO of Alexion Pharmaceuticals (New Haven, CT, USA), which collaborated in the study[1], said the results suggest that humanized mAbs might be effective treatments for conditions such as atherosclerosis, unstable angina and heart failure. The company has licensed patent applications on the mAbs from Brigham and Women's Hospital at Harvard University (Boston, MA, USA).

Complement activation pathways

Complement proteins are present in the blood in the inactive state. After activation, the end-product of the reaction cascade is a membrane attack complex that can puncture cell membranes, causing lysis or cellular activation. Until recently, there were thought to be two complement activation pathways: the classical pathway, which requires antibodies for activation, and the alternative pathway, which does not.

In the 1990s, it became apparent that a third pathway exists[2] that is similar to the classical pathway but does not require antibodies for its activation. This pathway becomes activated when mannose-binding lectin (MBL) binds to carbohydrates on the surface of microorganisms. MBL is a large molecule (≈600 kDa) and is similar in structure to C1q, the first molecule of the classical complement cascade. As with C1q, MBL circulates in association with inactive serine protease enzymes.

Complement activation in oxidative stress

Research during the 1990s showed that complement activation occurs on the endothelial cell surface after hypoxia/reoxygenation[3]. This type of model aims to emulate what occurs in the heart during a myocardial infarction. Gregory Stahl (Associate Professor of Anesthesiology and Physiology, Brigham and Women's Hospital) said, 'We had identified that the classical pathway of complement activation was involved, and thought that all we would need to do would be to isolate the antibodies deposited on those endothelial cells and purify the antigen that they were binding to.'

Unfortunately, Stahl and his colleagues were unable to find any difference between the quantity of antibodies on the endothelial cells that had suffered oxidative stress, compared with those that had not. After searching the literature for a possible explanation, they decided to investigate whether the lectin complement pathway was involved. Only a few inhibitors of MBL were available at that time, and one such inhibitor, mannose, successfully inhibited the complement activation[4]. The team therefore designed mAbs that would inhibit MBL. Stahl added, 'We thought that these mAbs could have some therapeutic use if we could establish that this pathway plays a role in human disease.'

In a recent paper[1], Stahl and his colleagues describe how they subjected endothelial cell cultures to hypoxia/reoxygenation, before adding a source of complement proteins such as human serum. They then washed the cells before measuring MBL levels on the cell surface using an MBL-dependent C3 deposition ELISA. They found that MBL was present and the lectin complement pathway activated in cells that had undergone hypoxia/reoxygenation, but not in control cells. They also showed that novel anti-MBL mAbs could inhibit both MBL deposition and lectin complement pathway activation. Stahl said, 'These antibodies could be used to treat any disease where activation of the lectin pathway is involved, or that is

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associated with oxidative stress to endothelial cells, such as stroke, gut ischaemia, kidney ischaemia or lung ischaemia. Currently there are no other therapies that inhibit the lectin complement pathway activation.'

Commenting on the study, Malcolm Turner, Professor of Molecular Immunology and Head of Immunobiology at the Institute of Child Health (University College London, London, UK) said the findings were 'extremely interesting and underscore the possibility that important pathological consequences might be associated with MBL-mediated complement activation.' He added, 'Research on MBL is, however, still in its infancy and much remains to be elucidated about the protein and its disease associations.'

Turner highlighted that another recently published study concluded that severe atherosclerosis is associated with MBL deficiency[5]. He said, 'The authors of this paper have interpreted this as possible evidence implicating chlamydial infections in coronary heart disease, because MBL is known to bind to various strains of *Chlamydia*. The findings from the two studies serve to emphasize the fact that the role of MBL in health and disease is more complex than was first anticipated.'

Future projects

Stahl's next project is to map the epitope of the mAbs, to determine how they inhibit MBL. 'We are also generating mAbs to the MBL of other animal species, so that we can use animal models of human disease to firmly establish what we have discovered *in vitro*,' Stahl said. 'We are further characterizing what MBL is binding to, so that we can develop novel inhibitors to that molecule.'

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Sharon Kingman

SNPs; windows of opportunity in the human genome

In April, the SNP Consortium issued a Request for Applications to determine how frequently single nucleotide polymorphisms (SNPs) occur in major human population groups (e.g. Caucasian, Afro-Caribbean). SNPs are single base pair (bp) differences that occur between individuals, such as the variations that lead to different blood types or the inheritance of the different alleles APOE3 or APOE4, both involved in susceptibility to Alzheimer's disease[1].

Although the majority of SNPs do not produce obvious physical changes or cause disease directly, they might be located close to deleterious mutations in the genome that are involved. Furthermore, because they occur at a

relatively high frequency in the genome (approximately one SNP for every 1000 bp), SNPs can be used as markers for these more important genetic alterations. 'The full genome SNP map will allow geneticists to identify areas of interest in the genome much more precisely than has been possible,' says Arthur Holden, CEO of the SNP Consortium.

SNP mapping targets

The SNP Consortium is a private, non-profit alliance of 13 leading multinational pharmaceutical companies and the Wellcome Trust (London, UK). It was established in April 1999 with a budget of $45 million and a two-year programme to identify 300,000 SNPs and to map at least half of them. Although the first year's target was to identify just under 100,000 SNPs, Holden confirms that 'outstanding progress has been made, primarily due to the use that we have been able to make of the constantly updated public draft of the human genome.' By April 2000, 149,000

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