NEURODEGENERATIVE DISEASE

Body-building for small molecules

Alzheimer's disease is the most common cause of dementia in the elderly, and, at present, there are no effective disease-modifying treatments. A key pathological feature of Alzheimer's disease is the build up of β-amyloid (Aβ) in the early phase, making this process a promising target for therapeutic intervention. However, developing small-molecule drugs that prevent the aggregation of Aβ is highly challenging, because the binding energy that drives protein–protein interactions involved in such processes is often distributed over a large surface area. Reporting in *Science*, Graef and colleagues now describe an innovative strategy for creating molecules that overcome these difficulties.

The secret of this new strategy lies in the synthesis of small molecules that have dual functions. One end of the bifunctional molecule — which is small enough to reach its biological target — binds tightly to Aβ; the other end binds to a protein chaperone, thereby providing the necessary bulk to prevent Aβ aggregation. Graef and colleagues generated a compound that they dubbed SLF-CR, using Congo Red (CR), a small molecule that is known to function as an amyloid ligand, and a synthetic ligand for the FK506-binding protein (FKBP) chaperone family.

Several measures of inhibition showed that this molecule successfully blocked Aβ accumulation when combined with FKBP, in contrast to SLF-CR alone or CR/FKBP, indicating that recruitment of the chaperone is crucial for inhibition of toxicity. More importantly, the authors showed that this molecule prevented neurotoxicity of aggregated Aβ *in vitro*: Aβ samples treated with SLF-CR/FKBP were considerably less toxic than untreated samples or those treated with CR/FKBP.

Morphological examination of cultured hippocampal neurons that were treated with SLF-CR/FKBP showed that this combination not only blocked the formation of aggregates, but also prevented changes in

INFLAMMATION

Nicotine goes into septic shock

Sepsis is the third leading cause of death in the developed world and accounts for 9% of the overall deaths in the United States every year. Well known for being a mild stimulant, nicotine is able to improve survival in mice with established sepsis, according to research published in *Nature Medicine*.

Local inflammation is an important defensive response to infection or injury. The process normally leads to recovery from infection and to healing. However, if targeted destruction and assisted repair are not properly co-ordinated, inflammation can lead to persistent tissue damage. The control of inflammation is complex, involving positive and negative feedback, and is sensitive to context. When an infection spreads to the bloodstream, inflammatory mediators that effectively contain local infections lead to an overwhelming systemic inflammatory response — sepsis — that causes multiple organ failure.

The central nervous system is able to rapidly and directly modulate the activity of the immune system. This physiological mechanism is known as the neuronal anti-inflammatory system, and is mediated primarily by nicotinic acetylcholine receptors expressed on macrophages. Sensory fibres within the vagus nerve detect systemic inflammation; the brain responds with anti-inflammatory signals carried through efferent fibres of the vagus nerve, which terminates in most critical organs.

The high-mobility group box 1 (HMGB1) protein has recently been identified as a late-stage mediator of lethal systemic inflammation in sepsis, causing further stimulation of inflammatory mediators. In the current work, Ulloa and collaborators showed that acetylcholine, the principal neurotransmitter of the vagus, targets macrophages and other immune cells to inhibit the release of inflammatory mediators, such as tumour-necrosis factor-α and HMGB1.

Blocking the production of HMGB1 from macrophages could be a useful strategy to combat sepsis. The authors demonstrate that nicotine, a more selective cholinergic agonist than acetylcholine, suppresses HMBG1 release from macrophages *in vitro*. Nicotine also reduces HMBG1 levels in a mouse model of sepsis. Most importantly, the chances of survival are improved in established sepsis even when treatment is initiated after the onset of disease. Nicotine exerts its anti-inflammatory effect via a 'nicotinic anti-inflammatory pathway' by signalling through the α7 nicotinic acetylcholine receptor.

Nicotine has several side effects that make it unsuitable as a therapeutic, and so the authors are currently designing more specific nicotinic agonists to overcome these problems. The 'nicotinic anti-inflammatory pathway' could explain the therapeutic effect reported in clinical trials using nicotine for the treatment of ulcerative colitis, and suggests therapeutic potential for other inflammatory disorders.

Melanie Brazil

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cell morphology and cell death induced by Aβ toxicity. Finally, the generation of a series of bifunctional molecules with the aim of improving potency led to the discovery of an inhibitor that had an IC_{50} of ~50 nM — lower than that of CR by a factor of ~40, and of SLF-CR by a factor of ~6.

The development of further small molecules on the basis of this strategy might therefore lead to promising therapeutics for targeting an early, pre-symptomatic, pathological process in Alzheimer's disease. Moreover, this methodology might be generally applicable in other diseases in which it is desirable to target protein–protein interactions.

Alison Rowan

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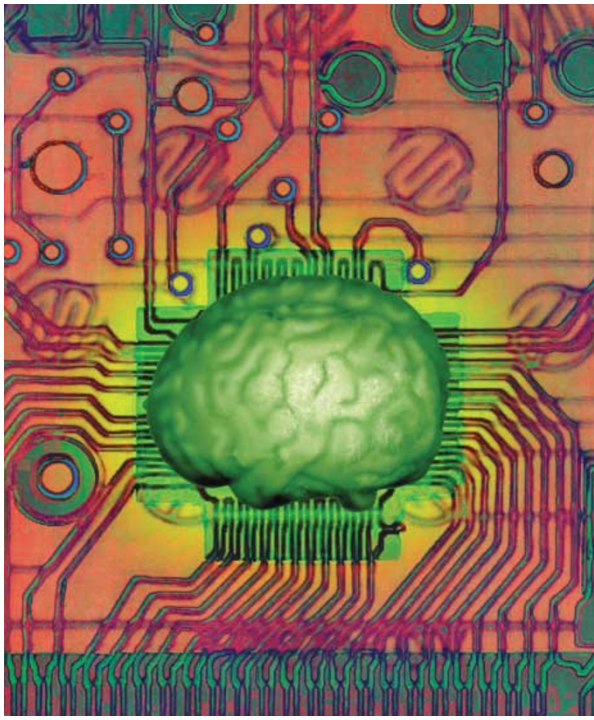
KINASES

Making gains on glioma



A small-molecule inhibitor of transforming growth factor-β (TGF-β) receptor I kinase could prove to be an effective treatment for human gliomas, according to a recent paper in *Cancer Research*. The investigational drug, SD-208, was shown to antagonize the immunosuppressive and pro-migratory properties that TGF-β exerts in cancer, and significantly prolonged the median survival of glioma-bearing mice.

Human glioblastoma is an aggressive form of brain cancer for which treatment options are limited and median patient survival is poor. TGF-β has become a key target in the search for more effective drugs because it is one of several immunosuppressive molecules commonly expressed by glioma cells. Although several approaches to inhibit TGF-β are being investigated, such as antisense and gene transfer, the identification of a small molecule that is more amenable to development as an oral drug would be desirable. Martin Uhl and colleagues report such a candidate molecule and describe its antagonistic effect on the biological activity of TGF-β *in vitro* and *in vivo*.

TGF-β exerts different biological effects depending on its cellular context and has roles in growth inhibition, immunosuppression and cell migration. The authors first determined whether SD-208 was an effective antagonist of TGF-β *in vitro* by demonstrating that SD-208 was able to reverse TGF-β-mediated growth inhibition of lung epithelial cells in a concentration-dependent manner. Moreover, SD-208 was able to neutralize the pro-invasive effect of TGF-β observed in assays of cell migratory activity, indicating that SD-208 could possibly prevent the further invasion of gliomas *in vivo*.

Perhaps most remarkable, however, was the ability of SD-208 to restore an immune response against glioma cells in culture. The lytic activity of peripheral blood lymphocytes or purified T cells was enhanced by co-incubation with SD-208 in a similar way to that observed with TGF-β-neutralizing antibodies, which confirms that the effect occurs through the inhibition of TGF-β. Furthermore, the inhibition of pro-inflammatory cytokine release and natural killer cell activation caused by glioma cells was reversed in the presence of SD-208, whereas release of the immunosuppressive cytokine interleukin-10 was inhibited.

Having established the efficacy of SD-208 *in vitro*, Uhl and colleagues then went on to study its potential anticancer effect in glioma-bearing mice. Measurement of TGF-β-dependent SMAD2 phosphorylation in mouse brain and spleen confirmed that SD-208 could inhibit TGF-β activity *in vivo*. Moreover, this inhibition correlated with a delayed onset of neurological symptoms in SD-208-treated glioma-bearing mice compared with untreated controls, and also a significantly improved survival rate after 30 days. These results were reflected by histological analysis, which showed a marked increase in immune infiltration in SD-208-treated mice that had smaller tumours compared with those that had larger tumours, indicating that SD-208 could attenuate the immunosuppression caused by TGF-β *in vivo*.

The authors conclude that treatment with TGF-β receptor-kinase inhibitors could prove useful to treat gliomas either alone or in combination with existing antisense therapies. Furthermore, SD-208 represents a potential new treatment paradigm in which neutralizing the effect of immunosuppressive cytokines secreted from tumours could be successful as an anticancer strategy.

Joanna Owens

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WEB SITES

The Hertie Institute for Clinical Brain Research: http://www.neurologie.uni-tuebingen.de

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