news

removed from the market after three cases of fatal progressive multifocal leukencephalopathy, a rare viral disease of the CNS. 'Currently, a huge safety update on the patients so far treated with natalizumab is taking place, and a new trial assessing safety is being planned. If the adverse event profile is better established, natalizumab may get a second chance to be approved for treatment of MS', says Neuhaus.

A long term effort

Reinhard Hohlfeld of the Institute for Clinical Neuroimmunology (Ludwig Maximilians University, Munich, Germany), who recently reviewed monoclonal development for MS therapy, was also disappointed that natalizumab ran into such problems. 'The history of drug development is beset with failures and MS therapy has provided some spectacular examples', he says wryly. Although therapeutic mAbs have shown much promise, several such potential therapies based on mAbs have had unexpected and unexplained severe side effects and, like Natalizumab, have had to be withdrawn, he adds. 'A new generation of neuroprotective and repair strategies, which might even reverse disability in MS patients, is on the horizon, but currently at a very early stage of development. With so many setbacks, it will be some years before we even come close to success', he concludes.

Medicinal mushroom cuts off prostate cancer cells' blood supply

Nicole Johnston, njohnston@rockefeller.edu

Ganoderma lucidum, a medicinal mushroom, is a widely popular dietary supplement in East Asia, taken to enhance health and longetivity. Its use in traditional Chinese medicine, including the treatment of cancers, is backed by two thousand years of anecdotal evidence and ever-increasing scientific data. Now, Daniel Sliva and colleagues at the Methodist Research Institute (www.clarian.org) and Indiana University in Indianapolis, IN, USA, (www.indiana.edu) have discovered how *G. lucidum* inhibits prostate cancer cell proliferation [1].

Potent anticancer agent

Triterpenes and polysaccharides are the biologically active components of *G. lucidum*, and are known to inhibit cancer growth and metastasis by modulating the immune system, inducing cell cycle arrest and triggering apoptosis. Sliva and colleagues have now discovered that *G. lucidum* halts prostate cancer cell proliferation by suppressing angiogenesis as well.

'My major interest is in how to stop the invasive behavior of cancers', explains Sliva, whose research focuses on identifying and characterizing anticancer compounds from nutritional sources. Indeed, previous studies by the authors showed that *G. lucidum* could suppress the movement and growth of highly invasive breast and prostate cancer cells and could trigger apoptosis and halt proliferation in prostate cancer cells.

In their latest study, Sliva and colleagues examined the effect of *G. lucidum* on prostate cancer cell angiogenesis. They found that mushroom extracts inhibited capillary morphogenesis (tube formation during angiogenesis) in human endothelial cells in a dose-dependent manner.

Suppressing angiogenesis

To study the effects of VEGF (vascular endothelial growth factor) and TGF-β1 (transforming growth factor), angiogenic factors involved in angiogenesis, they then added *G. lucidum* to prostate cancer cells and saw that it inhibited VEGF and TGF-β1 secretion in a dose-dependent manner, accounting for the inhibition of capillary morphogenesis.

Using *G. lucidum* preparations containing standardized amounts of triterpenes and polysaccharides, they then characterized how *G. lucidum* inhibits VEGF and TGF-β1 secretion by exerting its affects on both Erk1/2 and Akt signaling pathways, suggesting potential targets for therapeutic intervention. The result is inhibition of DNA-binding and activation of a transcription factor, resulting in downregulated expression of VEGF and TGF-β1.

***G. lucidum* extracts as chemotherapeutics**

'Since most of the chemical structures of *G. lucidum*'s antitumor triterpenes and polysaccharides have now been characterized, its chemopreventive and therapeutic potentials, mechanisms of action, efficacy and side effects should now be investigated', says Vay Liang W. Go, professor of medicine at UCLA (http://dgsom.healthsciences.ucla.edu/) in Los Angeles, CA, USA.

Sliva says they are currently focusing efforts on further characterizing and synthesizing these biologically active compounds responsible for the mushroom's anticancer properties. Yet, despite their promise, pharmaceutical companies are not currently taking any steps to develop these molecules as chemotherapeutics. 'They're interested but unlikely to vigorously pursue them since the bioactive phytochemicals in *G. lucidum* cannot be patented', explains Go.

If these compounds can be synthesized and thus patented, their development as actual chemotherapeutics seems likely, says Sliva. However, isolating the individual compounds and synthesizing them will prove to be an onerous task, he adds. In the meantime, he envisions *G. lucidum* as a dietary supplement and adjunct to cancer therapy. He and his colleagues anticipate beginning clinical safety trials in the next six months.

While *G. lucidum* can be obtained around the world and through the internet, Sliva advises that buyers beware. 'Not all (preparations) on the market have these active ingredients so the anticancer activity is not there', he says.

References

1 Stanley, G. *et al.* (2005) *Ganoderma lucidum* suppresses angiogenesis through the inhibition of secretion of VEGF and TGF-β1 from prostate cancer cells. *Biochem. Biophys. Res. Commun.* 330, 46–52

1359-6446/05/$ – see front matter PII: S1359-6446(05)03657-3