inaccurate reports of a supplement's safety and efficacy. He emphasized the need for extensive randomized clinical trials, similar to those already published for St John's wort and ginkgo biloba, which are necessary to distinguish between genuinely beneficial herbal supplements and those that have little medical value and pose significant toxicological risk.

A view from the USA

Varro Tyler (Dean and Distinguished Professor Emeritis, School of Pharmacy, Purdue University, West Lafayette, IN, USA) discussed how herbal remedies are regulated as dietary supplements rather than medicines in the USA. Manufacturers of herbal products in the USA are not allowed to claim that a product has a therapeutic effect. Moreover, they must state that any effect that the product might have has not been proven scientifically. The nutritional supplement market in the USA is swamped with products that vary greatly in quality, and a recent trend is the marketing of nutraceuticals, which are expensive foods containing only a small amount of herb extract.

Since its initial boom, the supplements market in the USA has been in decline (by 11.9% from 1998–mid-2000), which is thought to be because of reported side effects, drug–drug interactions, variable quality and limited evidence of efficacy. Tyler described how the lack of patent protection for supplements discourages clinical studies, and how only a few products have been adequately researched; the remainder is based on 'borrowed science'. This leads to a plethora of herbal products that are similar but inferior to well-researched products, which consumers find unsatisfactory, thus causing a decline in sales. Tyler suggested that a potential solution to this would be to approve herbal remedies as over-the-counter or prescription drugs with quality assurance.

Regulating the remedies

Michael Baker (Director of Legal and Regulatory Affairs, Proprietary Association of Great Britain, London, UK) discussed the existing regulations for herbal remedies in the UK, and what options were available for improving these. In the UK, a recent House of Lords report (http://www.parliament.the-stationery-office.co.uk) has outlined recommendations concerning the regulation of herbal remedies, the possibility of setting up centres of excellence for complementary medicine research and the provision of information sources and training for the public and healthcare professionals, respectively. With increased funding and research training, combined with effective regulation, herbal remedies could become an invaluable and safe addition to conventional medicine.

Acknowledgement

I would like to thank Edzard Ernst for his helpful comments on this article.

References

1 Ernst, E. (1999) Ginkgo biloba for dementia: a systematic review of double-blind, placebo-controlled trials. *Clin. Drug Invest.* 17, 301–308

2 Ernst, E. (1999) Second thoughts about the safety of St John's wort. *Lancet* 354, 2014–2016

A budding role for the UPR

Sharon Dorrell, Freelance writer

Activation of a stress signal transduction pathway – the unfolded protein response (UPR) – could play an important role in nitrogen-sensing in budding yeast. It could also be a weak point for attack by antifungal agents. Martin Schröder and colleagues at the Howard Hughes Medical Institute (Ann Arbor, MI, USA) suggest that the UPR is activated when there is a rich source of nitrogen and translation rates are high[1]. The UPR is responsible for transcriptional induction of 381 open reading frames in response to endoplasmic reticulum (ER) stress, including genes for ER-resident chaperones and ER-associated protein degrading machinery[1]. The team therefore proposes that high translation rates cause a build-up of unfolded polypeptide chains in the ER and UPR activation induces chaperones that promote protein folding and enable it to catch up with the supply of unfolded proteins in the ER. When nitrogen levels drop, translation rates decrease and the UPR is downregulated.

A protective mechanism

Down-regulation of the UPR also stimulates yeast to switch from normal, vegetative growth to either meiosis and asci formation (sporulation) or to filamentous pseudohyphal growth (the pathogenic form of many of these organisms)[1]. By switching to filamentous pseudohyphal growth, yeast can move and forage for a new nitrogen supply[2]. 'When the ER is stressed and contains unfolded proteins, the UPR has a protective function, and strains that can activate

1359-6446/01/$ – see front matter PII: S1359-6446(00)01673-1

the UPR survive higher levels of, for example, the antibiotic tunicamycin,' says Schröder. Tunicamycin and 2-deoxyglucose interfere with *N*-linked glycosylation and, therefore, inhibit protein folding and cause a build-up of unfolded polypeptide chains in the ER. Other drugs that inhibit protein folding in the ER are β-mercaptoethanol and dithiothreitol, which reduce disulphide bonds.

Deciding to switch

When nitrogen becomes limiting, say Schröder and colleagues, the decision to form asci or filaments depends on the carbon source. On a fermentable carbon source such as glucose, *Saccharomyces cerevisiae* switches to the more virulent, filamentous pseudohyphal form and its cells become elongated and switch to unipolar budding[3]. The cells also stick together and invade the agar on which they are growing, with both mother and daughter cells dividing simultaneously. By contrast, nitrogen starvation of yeast growing on a non-fermentable carbon source, such as acetate or ethanol, induces sporulation[2,4].

Schröder and colleagues found that either activation of the UPR or overexpression of the transcription factor Hac1^{1}p suppressed pseudohyphal growth in diploid yeast strains[1]. Hac1^{1}p is the product of an unconventional splicing reaction that bypasses the spliceosome and is modulated by the UPR. The reaction ceases when cells are starved of nitrogen but is reactivated when ammonium salts are added to the yeast culture.

New antifungal agents?

Schröder believes that because UPR plays a significant role in yeast differentiation, it is important for many physiological functions and defines a role for the UPR in nitrogen sensing. Furthermore, it shows that protein folding is not the final step in gene expression and that it can be regulated by the nutritional status of the cell. The team are currently investigating the molecular basis for repression of differentiation in yeast by the UPR. Although the research team are not currently investigating new drug candidates that could exploit the function of the UPR to treat fungal infections, Schröder says: 'drugs that impair protein folding in the ER, or otherwise activate the UPR, could serve as new lead structures in the search for new antifungal agents.'

References

1 Schroeder, M. *et al.* (2000) The unfolded protein response represses nitrogen-starvation induced developmental differentiation in yeast. *Genes Dev.* 14, 2962–2975

2 Gimeno, C.J. *et al.* (1992) The logic of cell division in the life cycle of yeast. *Science* 257, 626

3 Kron, S.J. *et al.* (1994) Symmetric cell division in pseudohyphae of the yeast *Saccharomyces cerevisiae*. *Mol. Biol. Cell* 5, 1003–1022

4 Donzeau, M. *et al.* (1999) The yeast trimeric guanine nucleotide-binding protein a subunit, Gpa2p, controls the meiosis-specific kinase Ime2p activity in response to nutrients. *Mol. Cell. Biol.* 19, 6110–6119