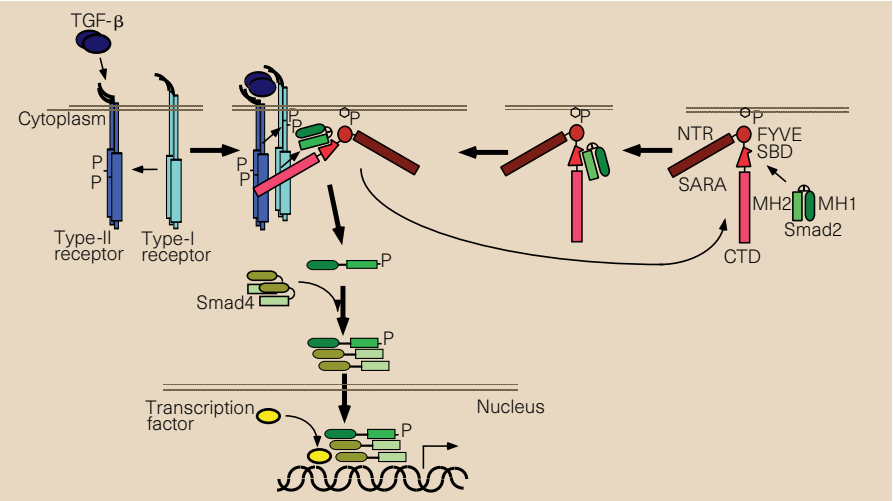

Figure 1 **Model for signal transduction in the transforming growth factor (TGF)-β/Smad pathway. Tsukazaki *et al.*[4] have identified a protein called SARA (Smad anchor for receptor activation) which, through adjacent binding sites for phosphatidylinositol-3-phosphate (PtdIns(3)P) and Smad2, recruits Smad2 to specific regions of the plasma membrane that also contain TGF-β receptors. SARA, Smad2 and the TGF-β–receptor complex cooperatively associate to form a transitional signal-transduction complex. After phosphorylation by a type-I receptor kinase, Smad2 dissociates and reassociates with Smad4 to form a heteromeric complex that translocates to the nucleus and regulates gene transcription. SARA is freed to recruit new Smads for activation by the type-I receptor kinase. NTR, amino-terminal region; SBD, Smad-binding domain; CTD, carboxy-terminal domain; MH, Mad-homology domain.**

containing the Smad, SARA and the TGF-β receptor is mediated through direct, cooperative interactions between these components. Smad2 and Smad3 are known[9,10] to associate with the activated TGF-β type-I receptor, and SARA is now shown to associate with Smad2 through an 85-amino-acid Smad-binding domain, located just on the carboxy-terminal side of the FYVE domain. In addition, SARA interacts through its carboxy-terminal domain with the TGF-β receptor complex, independently of Smad2 binding.

After Smad2 has been phosphorylated by the TGF-β type-I receptor, the components of the complex dissociate — the phosphorylated Smad has a lower affinity for both the receptor[9] and the Smad-binding domain in SARA. Phosphorylated Smad2 then forms a complex with Smad4, and translocates into the nucleus. SARA and Smad4 interact with the carboxy-terminal domain of Smad2 in a mutually exclusive manner[4], and once it has been released from the phosphorylated Smad2 molecule, SARA can recruit more non-activated Smad2.

Although SARA interacts with Smad2 and Smad3, Tsukazaki *et al.*[4] find that it does not bind to Smad1 — one of the receptor-regulated Smads involved in the bone morphogenetic protein (BMP) pathway. Considering the high mechanistic similarity between the TGF-β and BMP signal-transduction pathways, it is likely that Smad1 associates with a SARA-related molecule, and Tsukazaki and co-workers have identified two such candidates. Remaining questions include whether SARA binds directly to type-I or type-II receptors, or whether it binds to receptors other than TGF-β receptors. If SARA does not bind to activin receptors, it may provide an explanation for the differences in biological responses of TGF-β and activin, which can potentially activate the same Smads. Furthermore, SARA may have a scaffolding function by interacting with other components, such as other receptor substrates.

Tsukazaki *et al.* have shown that SARA is a critical component in TGF-β signalling, recruiting Smad to the TGF-β receptor. SARA may increase the efficiency, as well as the selectivity, of receptor signalling by favouring the phosphorylation of particular substrates and preventing unwanted crosstalk with other pathways. Control of TGF-β signalling may thus involve modulating the levels and subcellular distribution of SARA, or regulating the interactions between SARA and the TGF-β receptor and/or Smad. Finally, SARA — and similar molecules that present substrates — may be useful targets in screening for pharmacological compounds that inhibit TGF-β/Smad signalling. □

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Daedalus

A cultured brain

In the past 40 years or so, drug therapy has revolutionized psychiatry. Ideas about complexes, sublimation, super-ego conflicts and so on, have been replaced by concerns for neurotransmitter deficits, endorphins and receptors. But drug therapy is still a crude business. New psychotropic drugs are largely chance products, and their effects and side-effects must be found out the hard way. Daedalus plans to advance the art.

He points out that brain cells can now be cultured *in vitro*. One pioneering study used mouse brain cells, encouraged to grow and divide by epidermal growth factor. (This makes sense; the skin and the brain both grow from the same primitive set of embryonic cells.) In the right environment, says Daedalus, such cultured cells should start to put out dendrites and axons, and make connections with each other. A petri dish bearing a single sheet of cells might be best; their axons could wander freely over the surface of the sheet.

This 'brain pan' of interconnected cells will have no long-range structure or order. But it should be a splendid test-bed for psychotropic drugs, and theories of brain function and dysfunction. Once the brain pan has fully grown, Daedalus will lower test electrodes to touch specific cells in its monolayer. A pulse will be injected into one electrode. The cells around it which fire in response will be identified, and their connections with the central cell will be traced. Then a drug, neurotransmitter or brain metabolite will be added to the culture, and its effect on pulse transmission will be noted.

At first Daedalus will seek to understand the effects of known drugs. He will then test the resulting theories by trying new ones. No test animals will need to be sacrificed or human subjects risked; the most drastic or speculative notions will be easily tried. In particular, he plans to use widely separated electrodes to impose electroshock therapy on the brain pan, and to look for collective epileptic seizures in it.

By damaging selected cells of the brain pan, and noting its responses, Daedalus hopes to gain insights into Parkinsonism, Alzheimer's disease, and the other dismal brain deteriorations. Will the surrounding cells try to make other connections? Will local stem cells differentiate to replace lost neurons? Can a drug, a growth hormone or implanted new cells encourage these processes? Positive answers will bring cheer to ageing citizens and State pension and health agencies alike.

David Jones