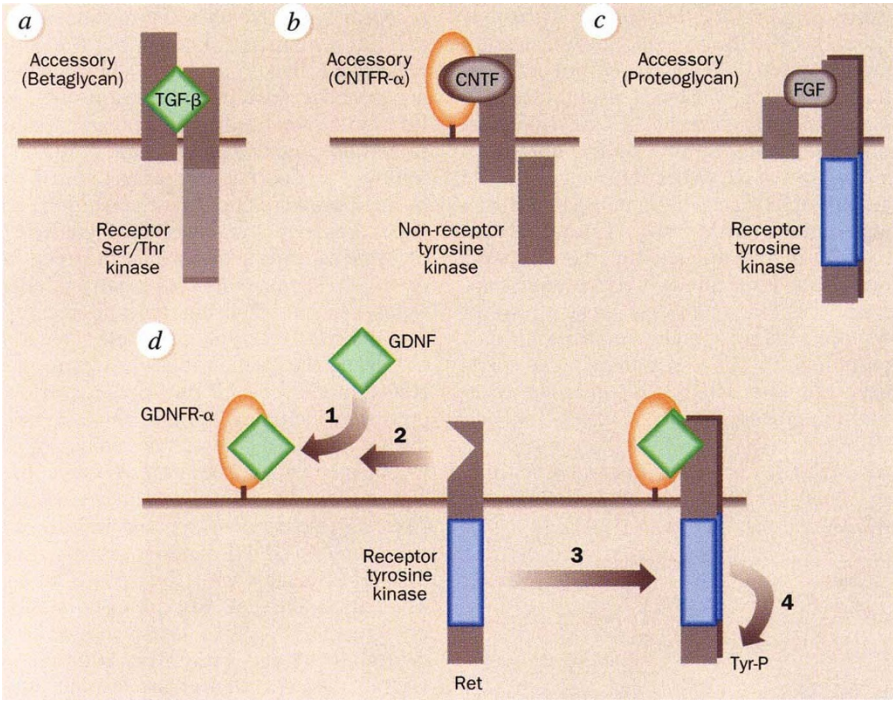

Comparison of signalling complexes of *a*, transforming growth factor-β; *b*, ciliary neurotrophic factor; *c*, fibroblast growth factor; and *d*, glial-cell-line-derived neurotrophic factor. GDNF is akin to members of the TGF-β family, but generates a complex with components of the other systems: it gains access to the tyrosine kinase Ret with help from a newly discovered entity, GDNFR-α, an extracellular protein that is attached to the plasma membrane by glycosyl phosphatidylinositol. In step 1, GDNF-α binds GDNF and, in 2, the complex is recognized by Ret. Upon formation of a stable complex between GDNF, GDNFR-α and Ret (3), Ret undergoes tyrosine phosphorylation (4), which leads to signalling. The special interest in the search for receptors for GDNF has stemmed from the earlier finding that this factor helps to promote the survival of dopaminergic neurons, failure of which is implicated in Parkinson's disease and other neuronal disorders.

The fact that a soluble form of GDNFR-α still allows GDNF binding to Ret suggests that GDNFR-α may force GDNF into a shape that can be recognized by Ret. The function of GDNFR-α clearly goes beyond limiting diffusion of a ligand: in essence, it appears that the Ret ligand is GDNF bound to GDNFR-α.

What is also remarkable about GDNF is that it is a TGF-β family member, but one that signals through a receptor tyrosine kinase rather than a serine/threonine kinase. This breach of a family tradition may reflect GDNF's status as the most distant TGF-β relative known to date. Its formal inclusion in this family hinges on the facts that GDNF has TGF-β-like precursor structure and dimeric subunit composition, and that it contains a set of cysteines typical of the family[1]. These cysteines form three disulphide bonds interlocked into a tight structure known as the 'cystine knot'[12]. To be sure, however, the cystine knot is not exclusive to the TGF-β family. Versions of this structure are present in nerve growth factor (NGF) and platelet-derived growth factor (PDGF), both of which signal through typical receptor tyrosine kinases, and in human chorionic gonadotropin, which signals through a G-protein-coupled receptor[12].

The cystine knot is one of the various core structures found in polypeptides that function in the extracellular milieu. As a group, the receptor tyrosine kinases have evolved to accept a wide range of such structures as ligands. With this in mind, GDNF could be viewed as just another structure recognized by receptor tyrosine kinases (in this case, a TGF-β-like structure). On the other hand, GDNF might be less of a TGF-β family renegade than it seems. Could some TGF-β family members signal through receptor tyrosine kinases as well as through receptor serine/threonine kinases? When the latter receptors took centre stage in this field a few years ago, any thoughts of tyrosine kinases being involved in TGF-β signalling faded away. It may now be time to explore those thoughts again. □

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DAEDALUS

Free-flowing salt

THE electrochemical salt bridge is an open glass tube containing a solid agar gel loaded with salt. The ions in the gel are quite mobile, so the bridge allows current to flow between two solutions while not allowing them to mix.

Daedalus is now generalizing this idea. Some ion-exchange resins are said to conduct electricity feebly; their absorbed ions can hop through the resin from one charged site to another. He suspects that in fact they are excellent conductors. Their high resistance arises only at the metal terminals of the test meter; the ions cannot travel through metal or transfer their current to it.

So DREADCO physicists are extruding ion-exchange resins into wire, and making transformer windings from it. Joining the ends will give a complete resin circuit, with no metal anywhere to block the current. As a secondary winding to a conventional transformer, the resin should be able to carry huge currents, maybe even approaching superconducting intensities — especially at high frequencies. For the higher the frequency, the shorter the distance each ion has to run before reversing its path. Indeed, at frequencies of many megahertz, the heavy individual ions will merely be shifting their weight from one foot to the other, so to speak. Scattering, the major source of resistive loss, will be almost negligible.

At the same time, DREADCO chemists are seeking better resins. Their models are the zeolite molecular sieves, and compounds such as urea and polyvinyl alcohol, with long canals through their structure capable of accepting guest molecules and ions. Their goal is a highly crystalline parallel-chain polymer with channels down which ions can flow as freely as possible. Cunningly, they are choosing long, thin ions (such as azide and triiodide), slightly mismatched to the lattice spacing of the polymer. They will find no well-fitting sites on which to bind, so they will move freely and losslessly through the lattice.

The final product should be a set of resin conductors as good as metal. Novel semiconductors, inhabited not by mere holes and electrons, but by a whole rich lattice-fauna of ions, should be possible. An ionic channel in a resin lattice could be blocked by one molecule sitting on the opening, thus creating an ultra-sensitive new chemical or biochemical sensor. Indeed, ionic resins are closely analogous to nerve membranes; and Daedalus wonders what the new ionic currents will feel like. Instead of the usual unpleasant electric shock, they may induce far more informative and rewarding sensations.

David Jones