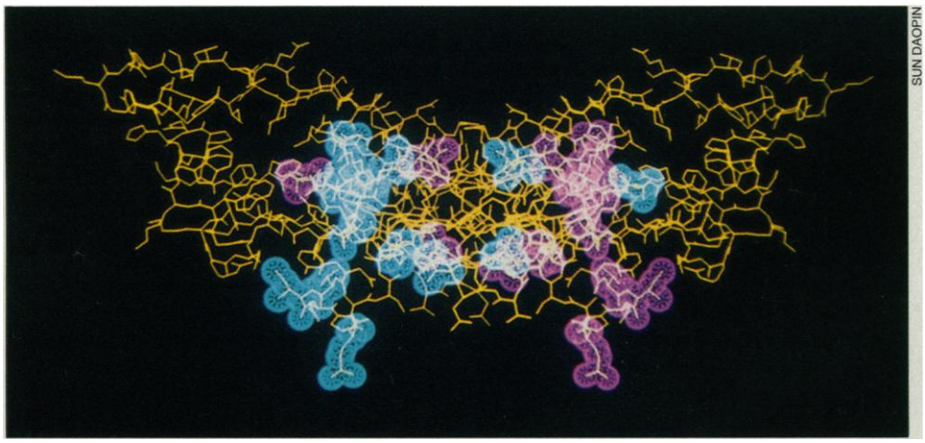

SUN DAOPIN

Possible binding sites. The colored amino acids (blue from one chain of the dimer, pink from the other) may form the sites that bind TGF-β to its receptors on the cell surface.

PROTEIN CRYSTALLOGRAPHY

Researchers Get a First Look at the Versatile TGF-β Family

In the past decade, cell biologists have discovered a myriad of signaling molecules that do everything from transmitting nerve signals to determining the body plan of developing embryos to controlling cell growth. But few of those biochemical players are more versatile than transforming growth factor-beta (TGF-β) and its relatives. Not only are these proteins important regulators of development and cell growth—they both stimulate it in some cells, as the name suggests, and inhibit it in others—they're also capable of promoting wound healing and bone reformation. And that's just a partial listing of TGF-βs' actions. Researchers have been wondering how a single group of messengers could play all those roles. And now comes a development that may help them understand this puzzle—as well as possibly lead to a host of applications for the pharmaceutical industry.

On page 369, Sun Daopin, Karl Piez, and David Davies of the National Institute of Diabetes, Digestive, and Kidney Diseases and Yasushi Ogawa of Celtrix Pharmaceuticals Inc. in Santa Clara, California, report that they have solved the three-dimensional structure of TGF-β2, the first member of the family for which that's been done. The structure, predicts crystallographer Davies, will likely serve as a prototype for all 18 members of the TGF-β superfamily. Meanwhile, Markus Grütter and his colleagues at Ciba-Geigy in Basel, Switzerland, who earlier this year reported the crystallization of the protein and some preliminary structural data, have also solved the TGF-β2 molecule. The Ciba-Geigy's groups results are in press at *Nature*, and the two structures have not yet been directly compared, but Grütter said the molecular dimensions reported by the Davies group sound identical to his.

The TGF-β2 structure came as a big surprise to experts in molecular form. The reason: This molecule, which seems to have something for everyone from physicians to cell biologists, departs from many of the rules that govern the folding of most proteins, Davies says.

As crystallographers and structural biologists have become increasingly skilled at determining the shapes of molecules, they have discerned that the same patterns repeat themselves in proteins of very different functions. The soluble proteins found in the watery medium in and around cells usually fold up in a compact, roughly spherical shape, Davies points out. The hydrophobic amino acids, which don't dissolve easily in water, end up in the inner core of the sphere, while the hydrophilic amino acids, which can easily interact with water molecules, are found on the outside.

But the TGF-β2 structure differs unexpectedly from this scheme, says Davies. Rather than forming a compact globular protein, TGF-β is somewhat extended, like an outstretched hand with only two fingers, which are slightly curled. Hydrophobic patches occur on the heel of the hand and near the finger tips, so that when two identical TGF-β molecules bind together to form a dimer, which is the form the active molecule takes in living organisms, the hydrophobic heel of one molecule touches the hydrophobic finger tips of the other, and vice versa. And in the center of this dimer, is one of the bigger surprises of this configuration—a cavity filled with four molecules of water.

In other multisubunit proteins, says Davies, the subunits usually abut each other, forming a continuous interface between subunits. "None of this," says Davies, "could have been anticipated by the sequence information." Nevertheless, Davies and his colleagues have found that certain portions of the molecule, key to giving TGF-β its characteristic shape, are retained in other members of the TGF-β superfamily. The group therefore anticipates that those molecules will probably have very similar structures.

Finding this structure should provide researchers with a much-needed boost in understanding the multiple activities of TGF-β. One key to understanding these activities is the interaction between the TGF-βs and their cell-surface receptors that initiates the cellular responses. And having the three-dimensional structure should help to elucidate this interaction. Molecular biologists Michael Sporn, Anita Roberts, and their colleagues at the National Cancer Institute (NCI), in collaboration with the Davies group, have already tentatively identified a set of 14 amino acids on the back of the TGF-β2 "hand" that may either bind the protein to its receptor directly or allow the protein to bend so binding can occur. Davies also wants to go the current work one better and solve the structure of the receptor–TGF-β2 complex. The structural work should not only provide the first link in a very complicated signaling network but may also pave the way to the development of new drugs.

Indeed, molecular biologist Joan Massagué of the Howard Hughes Medical Institute at Memorial Sloan-Kettering Cancer Center in New York, who was a member of one of the groups that described TGF-β2 in 1987, argues that discovering the molecule's structure will turn out to be a major boon to pharmaceutical companies, which have a keen interest in the TGF-βs because of their potential as targets for therapeutic drugs. There's evidence, for example, that inability to make TGF-β, or to respond to its growth inhibitory effects, may contribute to the development of some kinds of cancer, including breast and lung cancer. So drugs that mimic TGF-β's growth inhibitory effects might be useful in cancer therapy.

The pharmaceutical industry is also interested in developing drugs that can mimic the TGF-βs' promotion of wound healing and bone reformation. And knowing the structure should help in the development of such drugs, says Sporn, who with Roberts and their NCI colleagues purified and characterized the first member of the family, TGF-β1, in 1983. Because researchers will now "have a better idea of the fit between TGF-β and its receptor," says Sporn, potential therapeutics can now be designed on a "firm rational basis." And in the end that could be of great benefit to patients suffering from a very wide range of diseases.

–Michelle Hoffman