mispairing of bases will occur. Such a situation may be analogous to that in DNA which is damaged by mutagens; the same or similar repair mechanisms may operate, and these, by adjusting the base sequences in order to restore normal base pairing, would bring about gene conversion in the absence of any genetic replication. The model indicates how precise breakage and rejoining of chromatids could occur in the vicinity of the conversion, so that conversion would frequently be accompanied by the recombination of outside markers."[1]

Holliday proposed that this recombination intermediate arises from the nicking of one strand in each of two separate homologous DNA duplexes, followed by strand exchange to generate heteroduplex DNA in a four-way DNA junction (Fig. 1). We now know that this latter structure can also be formed by other means (such as the repair of double-strand breaks) and can be recognized by specific proteins that promote recombination.

Holliday's model was quite insightful, especially given that the molecular structure of DNA had been deduced only ~10 years before and that suggestions of enzymatic repair pathways for DNA were still in their infancy. Other models of recombination[2,3] followed, refining the basic strand-exchange proposal and propagating the common name of Holliday's proposed four-way junction recombination intermediate — the Holliday junction. *Tracy Smith*

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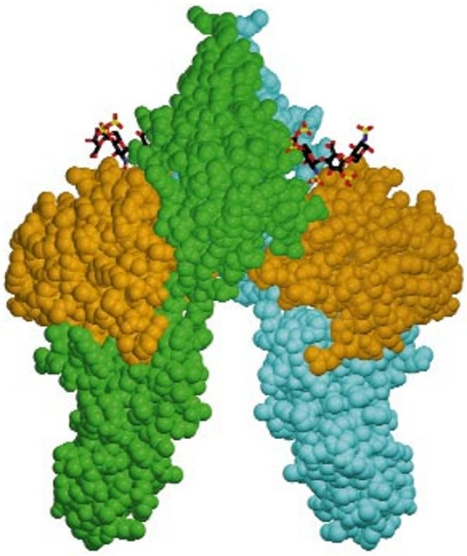
Dimers can do the deed

Members of the fibroblast growth factor (FGF) family act on a variety of mammalian cell types and play key roles in many biological processes, including cell growth, proliferation, differentiation and migration. The FGFs initiate signal transmission across the cell membrane by binding to the FGF receptors (FGFRs) and inducing changes in the oligomerization state of the receptors. The cytoplasmic domains of FGFRs possess tyrosine kinase activity. The oligomerization process brings these cytoplasmic domains into close proximity and allows phosphorylation *in trans* on Tyr residues, leading to receptor activation and phosphorylation of various downstream signaling molecules. While dimerization would intuitively seem to be sufficient for receptor autophosphorylation, it has yet to be demonstrated that a dimer is indeed the minimal signaling unit in this system, since receptor clusters in the cell membrane may actually be required for the activation process.

The fibroblast growth factors are monomeric proteins that are unable to induce receptor activation by themselves; rather, they function in concert with proteoglycans that contain heparin moieties to promote FGFR oligomerization. The recent crystal structure of an FGF in complex with the extracellular ligand binding domain of an FGFR (Plotnikov *et al.*, *Cell*, **98** 641–650; 1999) provides an important clue to the structural basis for FGFR activation by FGFs and heparins.



adapted from Plotnikov *et al.*

In the crystal structure, two FGF molecules (orange) bind on the opposite sides of the receptor dimer (green and cyan). Notably, the two FGF molecules do not directly contact each other. A positively charged canyon is formed between the top domains of the dimer of the receptor (behind the green FGFR subunit) and could accommodate a heparin molecule of various lengths. The ends of a heparin molecule of 12 sugar subunits manually docked into this canyon (ball-and-stick model, only the part of the heparin extruding from FGFR is visible) reach and interact with the FGFs.

The structure of the FGF–FGFR complex provides clues to how a heparin molecule and two FGFs stabilize the receptor dimer. The negatively charged heparin could interact with the positive charges lining both sides of the canyon, thereby facilitating dimer formation. In addition, the interactions between the heparin and the FGFs (as proposed in the model), together with the receptor–receptor interactions and the interactions between the FGF and the FGFR on opposite sides of the complex (as observed in the crystal structure), could further stabilize the dimer. The crystal structure of FGF–FGFR and the model of FGF–FGFR–heparin therefore suggest that dimerization is, in fact, sufficient for FGFR activation. Thus it is likely that an FGF–FGFR–heparin dimer is representative of the minimal structural unit required for transmembrane signaling by this family of growth factors. *Hwa-ping Feng*