dox in our understanding of how receptors activate G proteins: Experimentally identified contact points (*2*) of Gα with receptor (yellow) and Gβγ (orange and magenta) are more than 30 Å from the interdomain pocket that cradles GDP (red), suggesting that the receptor and βγ must "act at a distance" to catalyze GDP-GTP exchange. Definitive resolution of this paradox—a 3D structure of the receptor-Gαβγ complex from which GDP is released—will take time. In the meantime, we need to identify a mechanism that can transmit conformational change from one end of the protein to the interdomain cleft in the middle.

Differences between the GTPγS- and GDP-bound structures of α_{i1} (figure, compare upper left and upper right) indicate a route for transmitting just such a conformational change. The three Gα "switch regions" (cyan, green, and purple), first identified as sites of GTP-induced conformational change in α_t (*4*), are well defined in α_{i1}GTPγS (*6*). In contrast, two of these, switch 2 (green) and switch 3 (purple), are almost completely disordered in the GDP form of α_{i1} (*1*). In precise reciprocity, the amino and carboxyl termini are disordered in α_{i1}GTPγS but well ordered in α_{i1}GDP, presumably by their interaction (not shown) with the α-helical domain of the next monomer. The interdomain cleft is also affected, owing to lost contacts between the disordered switch 3 and the α-helical domain (*1*). Mixon *et al.* infer that the widening in α_{i1}GDP results from weak or broken contacts between the disordered switch 3 and the α-helical domain (*1*). Thus, structural stability and disorder of different parts of the protein appear to be concerted, with stability of the amino and carboxyl termini and disorder of two switch regions in α_{i1}GDP and exactly the opposite in α_{i1}GTPγS.

These apparently concerted, reciprocal transitions between order and disorder suggest a parallel scenario for action at a distance in G protein activation (see figure, lower panel): Like the next α_{i1}GDP monomer in the polymer, activated receptor and Gβγ bind to and stabilize the Gα amino and carboxyl termini, albeit in conformations that must differ from those depicted in the figure, for reasons outlined above. Stability of the termini in turn destabilizes switch regions 2 and 3 and alters the GDP binding pocket in the cleft. Rapid release of GDP probably requires a wider exit route (red arrow), which can be opened by displacing or creating disorder in switch 1 (cyan; removed in the lower panel). Such a change can plausibly be effected by Gβγ because allele-specific complementation in *Saccharomyces cerevisiae* (*10*) indicates a direct interaction between Gβ and a Gα side chain corresponding to that of His^{188} in α_{t1} (magenta), located just at the end of switch 1. After GDP escapes through the wider opening, GTP enters the empty site to complete the exchange reaction; its γ-phosphate reverses the conformational changes by reorganizing all three switch regions (*4*, *5*), reciprocally destabilizing the amino and carboxyl termini to promote departure of αGTP from Gβγ and the receptor, and in addition converting Gα into the right shape for stimulation of an effector.

This speculative scenario ties together several otherwise puzzling clues, although more detective work is clearly in order. The stakes are high because the molecular mechanism in question accounts for much of the regulatory and sensory information received by every cell.

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Remembering X-rays

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On the evening of 8 November 1895, Wilhelm Conrad Röntgen immediately recognized a remarkable new phenomenon. Fluorescent material lying on a bench some distance from the cathode ray tube with which he was experimenting lit up in his darkened laboratory. Like many others around the world, he was studying the beam of electrons emanating from the cathode in a low-pressure gas discharge (*1*). The electron beam could emerge from the thin window of the tube, where its range was a few millimeters, but fluorescence at a substantial distance was most surprising.

In fact, the fluorescence was not caused by electrons but by an entirely new form of radiation. Röntgen, 50 years old, and professor of physics at the University of Würzburg, went to work on this phenomenon with great intensity. He told no one about it until 22 December, when he told his wife and made the famous x-ray photograph of her hand. During the 7 weeks that followed his initial discovery, he did many careful experiments and wrote the results in the paper "Eine Neue Art von Strahlen" (*1*), calling the new radiation X-rays. He submitted it to the Sitzungsberichte der Physikalischen-medizinischen Gesellschaft zu Würzburg on 28 December, and within 4 days received printed copies of the publication. Röntgen refused to patent x-rays, preferring to put his discovery into the public domain for all to benefit. And indeed, the imagination of the public was captured by the ability to see bones in a living person and its obvious potential applicability to medical diagnosis (*2*).

On 23 January, at his first and only public lecture on the discovery, Röntgen made an x-ray picture of the hand of Dr. Albert von Kölliker, who in turn suggested that the new phenomenon be called Röntgen rays, the name used to this day in much of the world. The first attempt to treat cancer with x-rays was reported to have been carried out by E. H. Grubbe in Chicago on 29 January. The idea of using the technique to search baggage was put forward in a cartoon by the French *Journal La Nature* in May. At the same time, the harmful effects of the radiation became manifest very rapidly, with numerous injuries resulting from an almost complete lack of concern.

In 1896, Nobel prizes did not yet exist. However, when the prizes were first awarded 5 years later, Röntgen was the recipient in physics. Even today, 100 years after the discovery, we see continuing developments in x-ray sources (third-generation synchrotrons, x-ray lasers, and so on), as well as optical elements and detectors. These devices are opening up new fields in areas from microscopy to astronomy, from micromachining to the study of the dynamics of biological macromolecules. And so, this week we celebrate the centenary of a truly singular event in the history of science.

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