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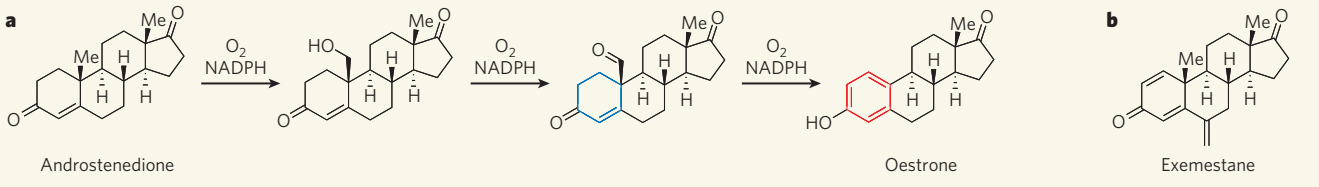

Figure 1 | Aromatase reactions. a, The aromatase enzyme catalyses a three-step process in which the steroid androstenedione is converted into an oestrogen molecule (oestrone). Each step requires oxygen (O_2) and a cofactor (NADPH). The final step is an aromatization reaction in which a non-aromatic ring (blue) is converted to an aromatic phenol ring (red). No other enzymes are known to catalyse aromatization reactions. Ghosh *et al.*[1] report the crystal structure of human aromatase in complex with androstenedione. **b,** Exemestane is an aromatase inhibitor that is used to treat a common form of breast cancer. Ghosh *et al.* show that it binds to aromatase in a slightly different way from the structurally related androstenedione, perhaps accounting for its inhibitory behaviour.

to many different substrates exhibit a looser fit, to accommodate more structural variety.

The structure conclusively reveals which amino acids form the active site, and which of those interact directly with androstenedione — information that previously could only be inferred indirectly. Ghosh *et al.* propose a mechanism for the aromatization reaction (see Fig. 3b on page 221) that is consistent with the observed enzyme–substrate interactions. Future studies to establish the details of the mechanism will require crystal structures for mutated versions of the protein, in which specific amino acids from the active site have been replaced with others. By observing the effect of such mutations on the function of the enzyme and on substrate–enzyme interactions, the precise roles of active-site amino acids in the normal enzyme can be determined.

Several clinical trials have compared the anticancer activity of state-of-the-art aromatase inhibitors (anastrozole, letrozole and exemestane) with that of tamoxifen[7]. The results indicate that aromatase inhibitors are more effective than tamoxifen at increasing the disease-free survival time of patients (the time interval between the initial diagnosis of cancer and recurrence of the disease following therapy) than in increasing their overall survival time (the lifespan after first diagnosis). The structure of exemestane is closely related to that of androstenedione (Fig. 1). Ghosh *et al.*[1] therefore modelled the binding of exemestane in the aromatase active site, and compared it with that of androstenedione. Although the binding of the inhibitor is closely related to that of androstenedione, the models also predict subtle structural differences. Specifically, part of the exemestane molecule becomes clamped in a hydrophobic part of the active site. This effect might lower the ability of a nearby amino-acid residue to initiate the formation of a reactive iron group in the active site. Such information could help to guide the development of a new generation of improved aromatase inhibitors, using existing compounds as a starting point.

One of the most remarkable aspects of the work[1] is that the structure was determined for native aromatase isolated from human placenta, rather than using a recombinant protein that had been artificially constructed using genetic-engineering techniques[8] (as is usually the case for X-ray studies). This is an advantage, as recombinant proteins are often truncated for practical reasons, so that a complete picture of the structure is lost. Ghosh and colleagues' native aromatase contains the hydrophobic 'tail' of the enzyme — a string of mostly hydrophobic amino acids at the amino terminus of the protein. *In vivo*, the tail extends through the phospholipid bilayer of the intracellular organelle known as the endoplasmic reticulum. Aromatase is the first example of a CYP protein that has been crystallized with its hydrophobic tail intact.

Ghosh and colleagues' structure will be vital for establishing the mechanism of the complex, three-step process catalysed by aromatase, particularly the biochemically unique aromatization reaction. But perhaps more importantly, it provides a roadmap for future drug-discovery efforts in the battle against the most common form of breast cancer. ■

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MOLECULAR BIOLOGY

A taste of umami

PAQUIN/PHOTOCUISINE/CORBIS

Of the five basic tastes — bitter, sweet, umami, sour and salty — umami is the least well known and certainly the least romantic. Yet most of us have experienced this savoury flavour, and commonly associate it with oriental cuisine. Xiaodong Li and colleagues now reveal the molecular mechanism behind perception of the umami taste (F. Zhang *et al. Proc. Natl Acad. Sci. USA* doi:10.1073/pnas.0810174106; 2008).

The umami taste comes from the amino acid glutamate, although ribonucleotides such as IMP and GMP greatly enhance its intensity. Like the sweet taste, perception of this taste depends on G-protein-coupled receptors of class C (C-GPCRs), which are found in cell membranes and also include many receptors of physiological importance. In C-GPCRs, a 'Venus flytrap' (VFT) domain, which binds to ligands on the cell surface, is connected to a transmembrane domain.

Although the receptors for the umami taste (consisting of T1R1–T1R3) and the sweet taste (T1R2–T1R3) share the same transmembrane subunit (T1R3), Li and colleagues show — using different combinations of these three subunits — that, in each case, the unique subunit mediates taste recognition. Moreover, four amino-acid residues deep inside the VFT domain seem to be essential for recognition of glutamate.

Enhancement of the umami taste by IMP/GMP, however, seems to depend on a different set of four amino acids in the opening to the VFT domain. So the authors propose that IMP binds near glutamate, supporting the ligand-bound, closed conformation of the VFT domain.

Regulatory molecules such as IMP that modulate the activity of GPCRs are of great interest to the drug industry — for example, they are more selective than agonist molecules, which might affect the activity of related receptors. As there are few known naturally occurring examples of IMP-like regulatory molecules, the significance of Li and colleagues' results goes beyond unravelling the mysteries of a curious taste.

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