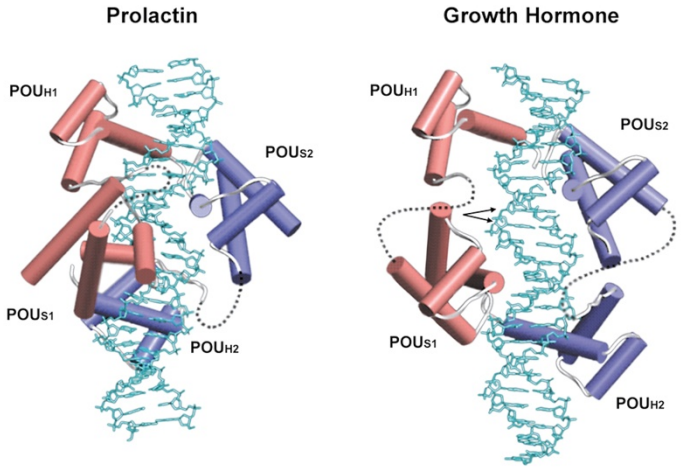
Milking it for all it's worth

Prolactin, the hormone that signals milk production in mammals, is made in a specific cell type called the lactotrope in the anterior of the pituitary gland. Although the lactotrope derives from the same lineage as that of the growth hormone-secreting cells (also in the pituitary gland), it does not produce growth hormone. It is thus an interesting question how closely related cell types are slated to perform these different tasks.

The expression of prolactin and growth hormone is regulated by a transcription factor, Pit-1, which is only expressed in the pituitary gland. Pit-1 contains a DNA binding domain (called the POU domain) that binds to sequences rich in A and T nucleotides. The promoter regions of both the prolactin and the growth hormone genes contain high affinity — but not identical — Pit-1 binding sites. This observation raises the question of whether subtle differences in the Pit-1 binding sequences of these two genes are sufficient to direct the hormone expression pattern in the lactotrope.

To address this question, Scully *et al.* (*Science* **290**, 1127–1131) first created transgenic mice to show that the Pit-1 binding sites in the growth hormone promoter are essential for restricting the growth hormone expression in the lactotrope. Specifically, when one of these sites (GH-1) was changed to a site from the prolactin promoter (Prl-1P), the lactotrope lost the ability to restrict expression of the growth hormone. To understand the structural basis of how these closely related DNA sequences control the hormone expression pattern, they determined the crystal structures of the Pit-1 POU domain in complex with the high affinity Pit-1 binding site in either the prolactin promoter region (Prl-1P; left) or the growth hormone promoter region (GH-1; right).



Adapted from Scully *et al.*

The Pit-1 POU domain binds DNA as a dimer (the subunits are labeled as 1 (red) and 2 (purple)) where each subunit is organized into two subdomains (POU_S and POU_H). Surprisingly, these two subdomains are accommodated very differently on the DNA in the two complexes: in the Prl-1P–protein complex, POU_S and POU_H of each monomer are positioned on perpendicular faces of the DNA (left), whereas these two subdomains occupy the same face of the DNA in the GH-1–protein complex (right). Most importantly, the spacing between the two subdomains changed from four base pairs in the Prl-1P–protein complex to six in the GH-1–protein complex (the insertion is indicated by arrows).

A close inspection of the Pit-1 binding sites in the growth hormone promoter reveals that the two-base pair insertion (sequence TT) is highly conserved across many organisms. The observed differences in the structures of the complexes may thus be important in specifying hormone expression in lactotrope. This hypothesis is further supported by experiments using transgenic mice which showed that in lactotropes, the GH-1 site with the TT insert deleted no longer restricts the expression of proteins under control of the growth hormone promoter. These results therefore suggest an 'allosteric' mechanism by which cell type specification could be achieved: subtle changes in the DNA sequences may modulate the structures of the DNA–protein complexes to mediate activated expression of prolactin and restricted expression of growth hormone.

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