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Transcriptional promiscuity in testes

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Numerous genes are expressed preferentially in spermatids, the haploid germ cells of the testis. Although some have defined, spermatid-specific roles, the expression and function of the products of most of these genes are not restricted to spermatids [1]. Examples include transcription factors that have defined functions elsewhere, kinases, metabolic enzymes, and so on. Recently, another group of proteins has been added to this list — the components of the basal RNA polymerase II (pol II) transcription machinery [2].

Recent reports suggest that the pol II machinery pre-assembles into a holoenzyme complex [3,4]. The levels of the components of this complex coordinately increase 30- to 100-fold during the early haploid stages of spermatogenesis ([2] and unpublished observations). Thus, early spermatid nuclei may have much higher concentrations of holoenzyme than do somatic cells. In this light, it is interesting to consider what would be the consequences of increasing holoenzyme levels by two orders of magnitude.

All models of transcriptional regulation to date include the assumption that the basal transcription machinery is constant and limiting; differences in the activity of a promoter between cell types have been presumed to result solely from differences in the 'attractiveness' of that promoter for a fixed concentration of pol II machinery. Promoter attractiveness can be regulated by altering DNA methylation, chromatin structure or transcription factor assemblages [5–7]. But changes in the concentration of holoenzyme might also alter the rate of transcription initiation at a promoter.

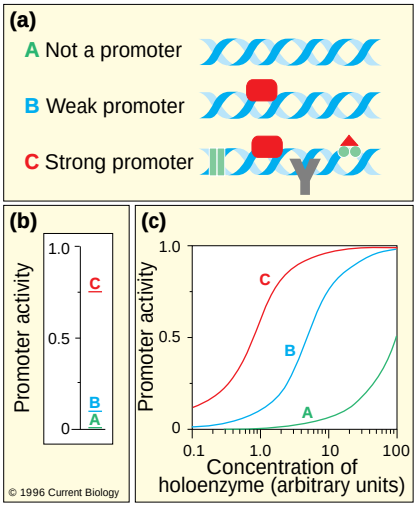
If the relative activities of the three promoters depicted in Figure 1a are plotted as a function of holoenzyme concentrations, each promoter gives a different activity curve (Fig. 1c). Thus, changes in holoenzyme concentration can affect the activities of various promoters differentially. For example, raising the holoenzyme concentration from 1.0 to 100 arbitrary units activates promoter C negligibly, whereas promoter B, which is a weak promoter at a holoenzyme concentration of 1.0, is now activated to the point of being nearly as strong as promoter C. Interestingly, at elevated holoenzyme concentrations, some DNA sequences that do not normally act as promoters — for example, promoter A in the figure — may now promote very strong transcription.

Is there any experimental evidence to support such a model? A recent paper [4] on mammalian RNA polymerase II holoenzyme showed that promoters which require transcription factors for maximal activity *in vitro* using crude nuclear extracts (which have relatively low holoenzyme concentrations) were highly active in the absence of such factors when supplied with a high concentration of purified holoenzyme. The addition of transcription factors did not further activate transcription, suggesting that at high holoenzyme concentrations, weak and strong promoters are similarly active. In other studies [3], purified yeast holoenzyme was shown to be responsive to activators. Figure 1c shows how, depending on holoenzyme concentrations, promoters might exhibit great differences in their response to activators.

What are the implications of this model for spermatid-specific gene expression? The model suggests that many genes which are expressed in spermatids might not require spermatid-specific transcription factors for their activation. Rather, early spermatids, by having elevated holoenzyme concentrations, may provide a permissive environment for transcription initiation. Thus, poor promoters in particular should have elevated activity in early spermatids (Fig. 1c). The model is consistent with the large number of genes that are expressed in the testis, and with the observation that testis-specific expression frequently involves both up-regulation of existing promoters and recruitment of additional promoters [1]. In contrast, genes for abundant spermatid-specific proteins have additional regulatory mechanisms to ensure that the difference in expression between spermatids and other cell types is orders of magnitude greater still [1,8].

The model proposed here does not suggest that genes which are expressed in spermatids, including those with known functions elsewhere, are expressed simply 'by

Figure 1



(a) Three hypothetical promoters with different assemblies of transcription factors. The dissociation constants for the interaction of each promoter with holoenzyme are set at 100, 5 and 0.5 arbitrary units for promoters A, B and C, respectively. The holoenzyme and the promoter complexes are assumed to be stable within the range of conditions modeled. (b) Relative promoter activities at a holoenzyme concentration of 1.0 arbitrary units. (c) Changes in holoenzyme concentration differentially affect the activities of the promoters without changing the affinities of the promoters for holoenzyme.

accident'. Rather, a mechanism is proposed that could activate transcription of numerous genes in spermatids. If a gene is transcribed and its protein accumulates in spermatids, it is very possible that the protein will function there.

Regulation of holoenzyme levels might also contribute to other cases of cell-type-specific gene regulation. Although no other cells seem to accumulate as much of the basal transcription machinery as early spermatids do, overall transcription rates do vary by more than an order of magnitude between different somatic tissue types [9]. Thus, differences in levels of the basal transcription machinery may be of wide-spread importance in determining patterns of cell-type-specific gene expression.

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Essay

Two hundred years of vaccination

Derrick Baxby

In a world in which infectious diseases seem once again to be on the increase, it is perhaps fitting that 1996 sees various events to commemorate the first documented smallpox vaccination, performed by Edward Jenner on May 14 1796 [1]. This article will consider Jenner's claim to fame and a few of the key events in the 200 years of vaccination that have followed his pioneering experiment.

Jenner has always been a controversial figure who polarized opinion, with even his supporters divided on whether he was a genius or a simple country doctor. That he preferred life in Gloucestershire rather than London is certain. Nevertheless, by 1796 he was a well-respected doctor-scientist, trained in London by John Hunter, with a general practice in Berkeley and a consultant practice in fashionable Cheltenham [2].

Jenner the naturalist

Although Jenner's name is inextricably linked with vaccination he should still have been remembered, particularly by zoologists, for his studies on bird behaviour, even if he had not developed smallpox vaccine. It had long been known that the female cuckoo lays her eggs in the nests of other birds. It was not known, however, how the eggs and nestlings of the foster parents were disposed of; the foster parents and the female cuckoo were variously thought to be responsible. In 1787, Jenner observed that it was the newly hatched cuckoo which ejected the eggs and nestlings of its foster parents; for this work he was made a Fellow of the Royal Society (FRS) in 1789 [2,3].

In these studies, Jenner was not content just to report observations: he tried to determine how and why the observed events occurred. For example, he described the anatomical modification to the back of the newly hatched cuckoo which facilitates its murderous activities, and which disappears within about 12 days of hatching. He also reasoned that the adult cuckoo laid its eggs in other birds' nests because it only stayed in Britain for about 11 weeks and would not have enough time to rear its young before it departed. At a time when some still believed that birds hibernated, he showed that the impulse to migrate was connected with changes in the reproductive organs and not due to climate or availability of food. With this analytical attitude it was perhaps inevitable that Jenner would become interested in the control of disease.

Jenner and smallpox

In the 18th century, smallpox was a major killer, leaving visible scars on many survivors. Its importance can perhaps most easily be appreciated by showing its effects on the family of King Charles I (Fig. 1). Attempts had been made for many years to control smallpox by 'variolation', the deliberate inoculation of smallpox virus into the skin in the hope that a mild but immunizing disease would result. There was a risk of severe smallpox for the inoculated and their contacts, however.

Jenner, an experienced variolator, became interested in the current folk lore concerning cowpox and smallpox in the late 1770s. The idea was that those individuals — traditionally milkmaids — who had recovered from cowpox could not later contract smallpox. Cowpox was a mild localized infection and Jenner collected circumstantial information that seemed to confirm the milkmaids' story. On May 14 1796, just before his 47th birthday, he inoculated 8 year-old James Phipps at two sites with material taken from the hand of a milkmaid, Sarah