RÉSUMÉ

Twinkle, twinkle

GRAVITATIONAL lensing may assist those searching for brown dwarfs, substellar objects that could account for much of the mass of our Galaxy. Because they are too small to 'burn' by nuclear fusion, brown dwarfs cannot be seen by their starlight, which is why they remain merely hypothetical. B. Paczyński reminds readers of the *Astrophysical Journal* (**371**, L63–L68; 1991) that the central bulge of our Galaxy is dense with slowly moving stars, and that as they pass behind the nearer stars in the galactic disk, gravity will focus their light to give us a brightened image. He points out that brown dwarfs could also focus background stars, though the brightening would not last so long (3–20 days instead of 1–4 weeks). In work in the press with *Astrophysical Journal*, Paczyński and S. Mao show that the same principle could be used to discover binary stars and remote planetary systems.

Bone hard

BONES are found far more often than soft tissue at archaeological sites, and offer a potentially huge harvest of DNA for the polymerase chain reaction – but only if the spectre of contamination can be exorcized. Hence the apparently inexhaustible capacity for taking pains shown by E. Hagelberg and J. B. Clegg in the isolation of mitochondrial DNA from a variety of bone samples (*Proc. R. Soc.* B**244**, 45–50; 1991). A pig bone from the larder of the *Mary Rose*, the ill-fated, sixteenth-century flagship of the English navy, for example, yielded DNA that is unequivocally porcine. Extracting DNA from bone, then, is not a problem, and the researchers recommend a stringent protocol to minimize spurious results from the exogenous DNA invariably associated with an archaeological sample.

Change for the worse

STUDIES reported by K. Hsaio *et al.* strengthen the case that damaged prion protein is at the root of several neurological diseases (*New Engl. J. Med.* **324**, 1091–1097; 1991). Some communities have an unusually high incidence of Creutzfeldt–Jakob disease, one such disorder, which has prompted several explanations of its cause, including the suggestion that consumption of the Mediterranean delicacy of sheep's eyes and brains is responsible. Hsaio and colleagues now confirm that an excess of the disease among Libyan Jews is more a result of genetics than of culinary taste: the disease occurs consistently in people in which a single amino-acid change has occurred within the prion protein, and the inherited genetic mutation seems to show complete phenotypic dominance in this population. The protein's normal function remains unknown, however.

GENE TRANSCRIPTION

TFIIB or not TFIIB?

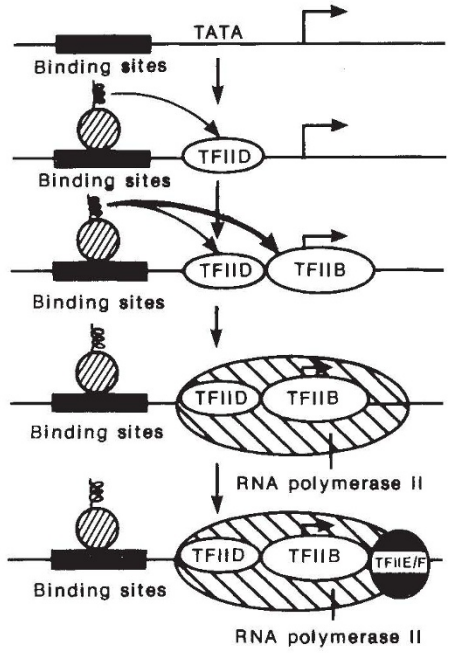
Phillip A. Sharp

LITTLE has been established about the mechanism by which sequence-specific DNA transcription factors stimulate initiation of transcription by RNA polymerase II (B). Two series of experiments now offer hope that this record will change. First, it is likely that transcriptional activation *in vitro* may be detectable only if the basal transcription reaction is repressed by chromatin, or more specifically by components of chromatin such as histone H1 (refs 1 and 2). Second, the major activation step in initiating transcription *in vitro* is probably not, as previously proposed, the template binding of the TFIID (TATA binding) factor, but the subsequent binding of the TFIIB factor to the TFIID–template complex[3]. This step forms the platform for the binding of RNA polymerase II and the TFIIE/F factor.

General transcription factors activate a basal reaction at the promoter site resulting in the positioning of the polymerase, and initiation. A distressing number of factors have been described as being important in this process. The simplest scheme is based on the assembly of template complexes which can be resolved by electrophoresis in native gels (see figure)[4]. The hallmark of this scheme is the ordered addition of factors where TFIID binding permits the association of TFIIA and TFIIB. Only after binding of TFIIB does the polymerase associate and the binding of polymerase is necessary for the association of TFIIE/F. This fraction is probably a mixture of two activities where the TFIIF component remains associated with the polymerase complex. Ideally, the rate of initiation of transcription reflects the rate-limited step in the assembly of this basal reaction.

Several sequence-specific transcription factors can bind to sites both proximal and distal to promoters and stimulate the rate of initiation of transcription. Because initiation requires the interaction of a number of basal factors with the TATA sequence and the polymerase, transcription factors are thought to increase the rate of the basal reaction. These factors possess one or more activation signals which, in theory, should promote the efficiency of binding or function of one or more of the basal factors that are rate-limiting for initiation by polymerase. The activation signals of transcription factors have been imprecisely defined as acidic, or proline- or glutamine-rich. Acidic protein domains that activate transcription possess a secondary structure, perhaps α-helical, and are apparently universally active in all organisms[5,6]. The acid-rich signal of the VP-16 protein of herpes simplex virus (HSV) has become the gold standard and has been analysed by mutations that change single amino acids. Both the acidic character and the conformation of this domain are important. Illustrative of the importance of conformation is that a single phenylalanine-to-proline alteration in the 78-amino-acid domain inactivates the signal[7]. Given the apparent simplicity and universality of the acidic activation signal, it was possible that a single universal step was accelerated by its activity.

Disappointingly, addition of transcription factors with activation domains to reactions containing highly purified basal transcription factors results in only a modest 2–5-fold



A model for how an acidic activator stimulates transcription. (Adapted from refs 3 and 4.)

stimulation of transcription – not the 100-fold stimulation observed *in vivo*. Interestingly, addition of the same transcription factors to a reaction containing a total nuclear extract could stimulate transcription 100-fold. The difference between these two results has been interpreted to mean that there is a coactivator that mediates stimulation of the basal reaction by the transcription factor (for review see ref. 8), the hypothetical coactivator being missing from the reconstituted reaction.

Alternatively, a change in the nature of the rate-limited step in initiation of transcription could explain the difference. For example, the association of a basal factor might be efficient, and thus not rate limiting, in a reaction reconstituted by purified basal factors, but inefficient, and thus rate limiting, in a reaction formed with a total nuclear extract. The stimulation by a transcription factor which promotes the binding of this basal factor will be much greater in the reaction containing the total extract. Comparison of the efficiency of transcriptional activation *in vitro* in the presence or absence of chromatin