could activate a Gal4-dependent reporter further in response to MKK6-induced p38α/β signaling. In fact, further activation of the reporter was not observed until either BRG1 or BRM was added back to these cells. These results provide compelling evidence that p38α/β does not signal directly to MyoD or affect its intrinsic remodeling activity.

Mef2 proteins cooperate with MyoD to induce gene expression[9] and are also targets of p38α/β signaling[2,5,10]. Could Mef2 proteins be mediating some of the observed effects? Notably, the truncated version of MyoD, which lacks the ability to associate with Mef2 (ref. 11), retains the ability to activate the reporter in the presence of BRG1 or BRM and p38α/β signaling. These findings argue against an essential role for Mef2 under the assay conditions used, but further studies are required to examine this question in detail.

### Pathways to activation

This study by Simone *et al.* provides evidence that the p38α/β pathway promotes muscle differentiation by indirectly signaling to MyoD through the SWI-SNF chromatin-remodeling complex, resulting in expression of *Myog* and *Ckm* (**Fig. 1**). Increasing evidence over the past few years suggests that, in addition to targeting transcription factors, kinases can alter gene expression by targeting chromatin-modification factors. Simone *et al.* have demonstrated this for the first time with the p38α/β pathway in muscle.

As p38α/β regulates only a small proportion of MyoD target genes[12], it will be interesting to determine if other promyogenic signaling molecules are responsible for recruiting chromatin modifiers to different loci. It will also be important to determine exactly how BAF60 phosphorylation influences the selective recruitment of SWI-SNF to specific target loci. Are all p38α/β regulated targets in muscle activated by this mechanism, or do Mef2 proteins mediate some of the observed effects of p38α/β signaling on muscle-specific transcription? Finally, it will be important to determine how this signaling mechanism influences muscle formation *in vivo*. Mutating the phosphorylated residue(s) of BAF60 or the residue(s) important for the interaction between BRG1 and MyoD, and targeting these mutants to endogenous loci in mice, could be used to determine the importance of this signaling mechanism in regulating the muscle differentiation program.


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# From proteomics to disease

Kenneth H Kraemer

**The nucleotide excision repair system is essential for repairing DNA damage caused by exposure to sunlight. Now, parallel studies in yeast and individuals with a rare disease called trichothiodystrophy have identified a new component of the DNA repair and basal transcription factor TFIIH.**

In 1968, James Cleaver described a defect in DNA repair in cells from three individuals with a rare disease called xeroderma pigmentosum[1] (**Fig. 1**). The DNA repair defect in these individuals resulted from a failure of the nucleotide excision repair (NER) system to remove photoproducts from DNA that is damaged by ultraviolet (UV) radiation. Individuals with xeroderma pigmentosum develop pigmentary abnormalities on their skin at an early age and have 1,000 times more sunlight-induced cancers of the skin and eyes[2]. Organisms as diverse as yeast and humans have NER systems composed of homologous proteins that function together to recognize DNA damage, unwind DNA in the damaged region, excise the damage to create a gap and fill in the gap using the undamaged strand as a template (**Fig. 1**)[2,3]. Defects in seven of these proteins (XPA–XPG) are associated with xeroderma pigmentosum in humans.

In 1993, a group led by Jean-Marc Egly, working to define the basal transcription factor TFIIH, reported that two TFIIH components were also DNA repair proteins: XPB and XPD[4,5]. In this issue, Jeffrey Ranish and colleagues[6] and Giuseppina Giglia-Mari and colleagues[7] report a new shared component of the DNA repair and basal transcription machinery, called TFB5, which is linked to a rare human disease called trichothidystrophy (TTD).

### A crucial link

The observation of Egly and colleagues established a crucial link between transcription and DNA repair, which explained why mice completely lacking XPB or XPD showed embryonic lethality, as TFIIH is essential for survival. Nevertheless, certain mutations in *ERCC3* (encoding XPB) and *ERCC2* (encoding XPD) are present in individuals with xeroderma pigmentosum and are compatible with survival[8]. There are varied clinical phenotypes associated with different defects in XPD and XPB in humans (**Fig. 1**). Some involve progressive neurologic degeneration, and others involve short stature, developmental delay and severe wasting (the xeroderma pigmentosum and Cockayne syndrome complex). These distinct manifestations seem to reflect defects in different functions of the same protein.

Several years ago, Miria Stefanini and colleagues observed that some individuals with defects in XPD or XPB have a phenotype known as TTD[9–11]. Cells from these individuals behave in culture like those of individuals with xeroderma pigmentosum, but the affected individuals themselves present a very different phenotype characterized by sulfur-deficient brittle hair, skin photosensitivity without increased pigmentation and

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no increase in cancer susceptibility[2]. In 1993, the same group identified an individual with TTD whose cells were hypersensitive to killing by UV but who did not have defects in XPB or XPD[12]. This result suggested that a gene other than *ERCC3* or *ERCC2* caused this same phenotype when mutated. Thus began a ten-year quest for the gene underlying this locus, *GTF2H5* (also called *TTDA*).

### The hunt for *GTF2H5*

Because XPB and XPD are components of TFIIH, this complex may also include the protein encoded by *GTF2H5*. Measurements of TFIIH showed low levels of this complex in cells from individuals with TTD-A[13,14]. But exhaustive sequencing of each of the nine known TFIIH components detected no mutations, and expression of each of the purified TFIIH proteins did not correct the cellular defect[13].

The turning point came with the work of Ranish *et al.*[6], who used proteomic techniques to identify a new component of TFIIH in yeast, which they called TFB5. Like cells from individuals with TTD-A, yeast cells deficient in TFB5 were hypersensitive to killing by UV. At the same time, it was noted that REX1S, a suppressor of UV-sensitive mutants in the alga *Chlamydomonas reinhardtii*[15], shared sequence homology with TFB5.

Inspired by these discoveries in yeast and algae, Giglia-Mari *et al.*[7], in collaboration with the Ranish group, asked whether the human homolog of TFB5 was defective in cells from individuals with TTD-A. Using a combination of cellular, molecular and biochemical techniques, they cloned the new human factor (TFB5, encoded by *GTF2H5*), found that it stabilizes the human TFIIH complex and showed that it can correct the DNA-repair defect, the UV-survival defect and the reduced TFIIH levels in cells from individuals with TTD-A. They also identified mutations in this gene in four individuals with TTD from three separate families.

### From bedside to bench

These papers illustrate the importance of studying rare human diseases, examining basic mechanisms of protein interaction in yeast and exchanging scientific information. Only three families with TTD-A have been identified, but they were key to discovering information about the function of the transcription machinery across all eukaryotes. Similarly, the new technique of quantitative proteomics for the study of macromolecular complexes[6] provided insight into important protein-protein interactions. The varied clinical phenotypes (**Fig. 1**) may result from altered interactions of the defective proteins with other proteins that control growth, development or cancer susceptibility. Notably, only some of the proteins listed in **Figure 1** are currently associated with clinical diseases. Furthermore, the clinical phenotypes associated with the known disorders are quite varied. Thus, it seems possible that defects in these proteins might underlie other rare diseases, with phenotypes that we can only guess at this time.

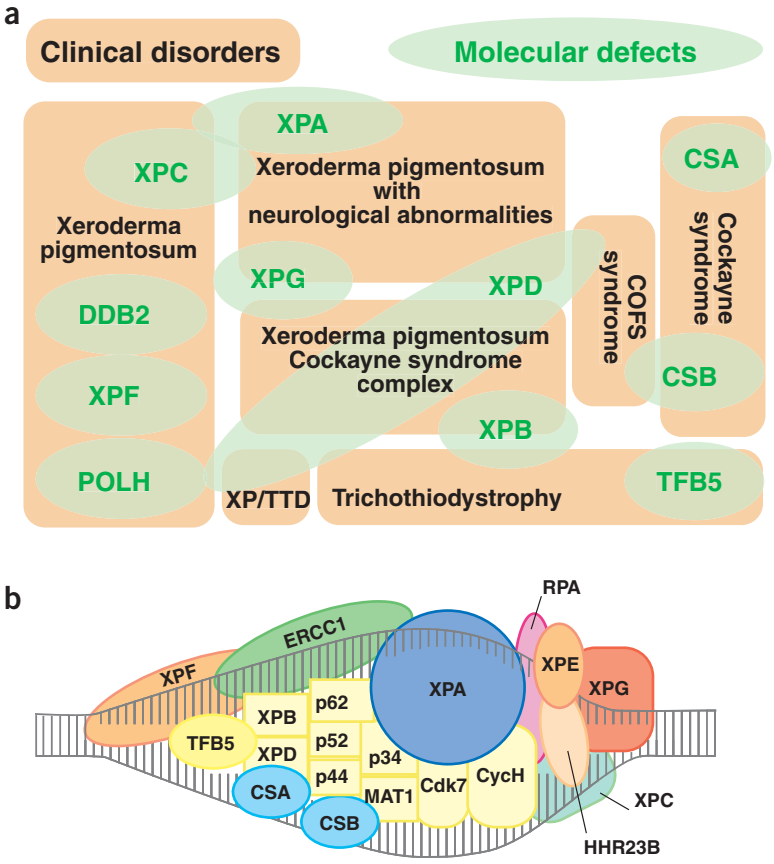


**Figure 1** Relationship of some rare human diseases to defects in proteins involved in DNA repair and transcription. (**a**) Seven human disorders (rectangles) share the phenotype of sun sensitivity but differ in their involvement of the skin, the nervous system, growth defects, developmental defects and cancer susceptibility. They are associated with defects in 11 genes (ovals). (**b**) The products of genes involved in the basal transcription factor TFIIH (yellow) interact with components of the NER system (other colors) to repair damaged DNA.


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