clear whether these are acquired antibodies that recognize infected red cells (*11*) or nonimmune IgG.

The new work raises several questions for future research. Protein A inhibits parasite adhesion although it does not bind to IgG3. This should prompt an investigation of isotype specificity in the interaction between DBL domains and IgG. The authors propose that it is the neonatal Fc receptor that is a placental receptor for infected red cells. However, several studies have concluded that the neonatal Fc receptor is not expressed on the syncytiotrophoblast surface (*12*, *13*), but instead is found in vesicles within the syncytiotrophoblast where it binds to IgG taken up by pinocytosis. Either the cellular localization of neonatal Fc receptors will need to be revisited, or consideration will need to be given to other surface molecules with Fc receptor activity. Furthermore, Fc receptors are expressed throughout the placental villus, so why did malaria-infected red cells coated with antibody adhere only to the syncytiotrophoblast surface? Fc receptors for antibody are expressed in other vascular beds—why would infected red cells coated with antibody be selected only by the placenta, and not by other tissues? Malaria may teach us something new about the accessibility or specificity of antibody receptors.

The helminth *Schistosoma mansoni*, a parasite of humans, is thought to adsorb host antibody onto its surface to avoid immunologic recognition (*14*). In a similar way, *P. falciparum* might benefit from IgG coating the red cells that it infects. If so, this would complement its other strategies for immune evasion, including antigenic variation, direct modulation of the host immune response, and, of course, deep vascular sequestration that permits the parasite to avoid clearance by the spleen. *P. falciparum* possibly emerged only recently as a human pathogen (*15*), but it has proven itself remarkably adept at adjusting to and manipulating its host.

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PERSPECTIVES: TRANSCRIPTION

Transcription Factor IID—Not So Basal After All

C. Peter Verrijzer

From skin and muscle to nerve and blood, our bodies are composed of more than 200 distinct types of differentiated cells. But how does this profusion of different cell types arise from a single fertilized egg? With a few exceptions, all of our cells contain identical genetic information, and thus the features of each cell must be determined by its pattern of gene expression, that is, which genes are turned "on or "off." The process that switches on the appropriate genes in the correct cells at the right time is, therefore, central to cellular differentiation and the development of multicellular organisms.

Gene expression is controlled predominantly by regulating transcription, the process that copies the gene's DNA instructions into messenger RNA (mRNA), which is then translated into protein. The molecular machinery that drives the transcription of genes comprises RNA polymerase II (the actual enzyme that makes mRNA) and a group of basal or general transcription factors (GTFs): TFIIA, B, D, E, F, and H (*1*). This basal transcription machinery assembles on a DNA sequence, termed the core promoter, located at the beginning of a gene. In addition, regulated gene expression requires DNA sequences, termed enhancers, that bind to sequence-specific DNA-binding proteins (activators), which in turn activate transcription (see the figure). Each gene is controlled by a unique array of binding sites for distinct activators that ensure its expression at the right time and place. The communication between the enhancer-bound activators and the basal transcription machinery depends on a third class of transcription factors, the so-called coactivators (*2*). It is generally believed that a universal, invariant basal transcription apparatus integrates the signals from enhancer-bound gene-specific activators expressed only in particular cells. However, with the flurry of recent papers (*3*–*9*), including one by Freiman *et al.* (*3*) on page 2084 of this week's issue, it is time to revise and extend this view. The new studies reveal that tissue-specific components of the basal transcription machinery can also be gene-specific regulators of development.

Surprisingly, these studies implicate tissue-specific TFIID-related factors in orchestrating two of the most extraordinary cell-differentiation programs in metazoan organisms, namely, the development of male and female gametes. During the formation of both eggs (oogenesis) and sperm (spermatogenesis) the precursor cells undergo meiosis, a type of cell division that reduces the double set of chromosomes to a single set. At the same time, there are dramatic changes in cell structure and morphology directed by stringently controlled stage-specific gene expression programs. The oocyte, the largest cell in an animal, is extensively prepared and intricately programmed to develop into a new individual. Sperm, on the other hand, are "stripped-down" motile cells tailored for the delivery of DNA to the egg.

TFIID is the prime sequence-specific DNA-binding GTF and forms the scaffold upon which the rest of the basal machinery assembles as a prelude to transcription (*1*). Consequently, binding of TFIID to the core promoter constitutes a critical rate-determining step and a key point at which activators can control transcription. TFIID comprises the TATA box–binding protein (TBP) and about 10 TBP-associated factors (TAF_{II}s) (*2*, *10*–*12*). TBP and most of the TAF_{II}s are highly conserved from yeast to human and are encoded by essential genes. TBP is important for binding of TFIID to the TATA-box; the DNA-binding TAF_{II}s recognize other core promoter elements, such as the initiator and the downstream promoter element (*13*). Selected TAF_{II}s are coactivators and are believed to promote transcription by acting as adaptors, linking activators to the basal machinery (*2*). Moreover, $TAF_{II}250$ harbors three distinct enzymatic activities that are all involved in transcriptional regulation (*2*). To complicate matters further, a subset of TAF_{II}s are also constituents of histone acetyltransferase (HAT) complexes that lack TBP (*11*, *12*).

The first hint of tissue-specific TFIID components was the discovery of $TAF_{II}105$, a subunit of TFIID, in a differentiated human B cell line (*14*). Cloning of

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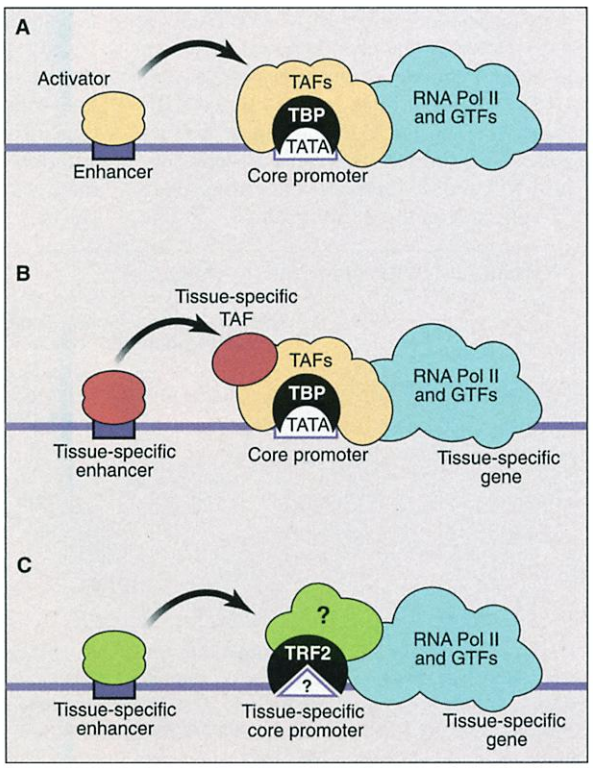
the corresponding gene revealed that $TAF_{II}105$ was related to a ubiquitous TFIID subunit, $TAF_{II}130$. In their new study, Freiman *et al.* inactivated the mouse gene encoding $TAF_{II}105$ by homologous recombination (*3*). Mice that lack $TAF_{II}105$ are viable, but the females are infertile owing to a defect in the formation of follicle cells that nourish the egg. A $TAF_{II}105$ deficiency did not affect B cells, suggesting that other TFIID subunits (possibly $TAF_{II}130$) can replace $TAF_{II}105$ in the immune system. In agreement with its importance during oogenesis, $TAF_{II}105$ is particularly highly expressed in the granulosa cells that surround maturing oocytes. A comprehensive gene expression inventory with oligonucleotide microarrays indicated that only about 1 in every 100 genes might require $TAF_{II}105$ for their expression in ovaries. Significantly, the strongly affected genes included several known to be essential for the normal formation of follicle cells. $TAF_{II}105$ is associated with TBP and $TAF_{II}250$, suggesting that it controls gene expression during female gametogenesis as a tissue-specific TFIID subunit.

These results complement the recent findings by Fuller and co-workers (*4*) who identified another TAF_{II} as a critical regulator of the gene expression program directing male gametogenesis in the fruit fly. Loss of the product of the *Drosophila cannonball* (*Can*) gene leads to a block in meiosis, preventing the initiation of spermatid differentiation. The *can* gene encodes a homolog of the ubiquitously expressed $TAF_{II}80$, a subunit of both TFIID and large TBP-free HAT complexes (*11*, *12*). In contrast to $TAF_{II}80$, *Can* is expressed in a strictly stage- and tissue-specific manner in primary spermatocytes. *Can* is essential for the expression of a range of genes required for spermatid differentiation, suggesting that it is a TAF_{II} specifically tailored to direct a tightly controlled developmental gene expression program.

Finally, a TBP-related factor, TRF2, has also been implicated in development. Although TRF2 is conserved from worm to human, TRF2 inactivation reveals that it has distinct jobs in different species. In frogs and worms, TRF2 deficiency leads to defective early embryonic gene expression and death (*5*–*7*); in contrast, *Trf2*-deficient mice are viable and undergo normal embryonic development (*8*, *9*). However, whereas *Trf2*-deficient female mice are fertile, the males are sterile owing to a severe defect in spermiogenesis (*8*, *9*). Indeed, an inventory of potential target genes reveals that several spermiogenesis genes require TRF2 to be transcribed normally.



Mix'n'match. (**A**) The pattern of expression of a typical gene is determined by tissue-specific or ubiquitous activators and the binding of the basal transcription factor TFIID to the gene's core promoter. (**B**) However, cell type–specific expression of some developmental genes depends on tissue-specific homologs of TFIID subunits including TAF isoforms, which might provide unique targets for tissue-specific activators. (**C**) In addition, expression of certain developmental genes may depend on TRF2, a TBP-related protein that binds to core promoters of a subset of genes that are not recognized by TFIID.

Collectively, these studies demonstrate that there is not a single invariant TFIID complex directing all RNA polymerase II transcription. Instead, there are multiple tissue-specific TFIID-related factors that are important in the developmental regulation of gene expression. This is reminiscent of prokaryotic sigma factors that direct RNA polymerase to selective promoters. According to what is already known about their ubiquitous homologs, it is tempting to speculate that TFIID-related factors may selectively promote transcription. For example, a granulosa cell–specific TFIID complex containing a $TAF_{II}105$ may be selectively recruited by a cell- and stage-specific activator. Because TRF2 fails to recognize the TATA-box, it may bind to specific core promoters not recognized by TBP (*15*). It will be interesting to test potential target promoters for such putative TRF2-binding elements. Moreover, TRF2 appears to be part of a larger complex (*15*) and may be associated with TRF2-specific TAF_{II}s. Finally, *can* protein may be a component of a tissue-specific TFIID or of a TBP-free HAT complex, or it may even associate with TRF2.

Although some ubiquitous TAF_{II}s are required for the transcription of a large number of genes, others are gene-specific (*2*, *11*, *12*). Mutant forms of these TAF_{II}s block specific gene expression programs and developmental processes (*2*, *11*, *16*). Thus, an individual TAF_{II} cannot simply be equated with the complex in which it resides. Rather, different TFIID subunits seem to provide distinct activities required by specific subsets of genes.

Analysis of tissue-specific TFIID-related factors exemplifies how complexity in biological systems evolves by accretion and modification of preexisting components. In addition to the TAF_{II}s discussed here, genome-sequencing projects have uncovered other TAF_{II}-related genes. Strikingly, whereas yeast cells contain single isoforms of each of the components of the general transcription machinery, animal cells have homologs of several TFIID components as well as TFIIA (that shares many properties with TAF_{II}s) but not of the other GTFs. Thus, among the GTFs, TFIID components appear to have been singled out for diversification during evolution to broaden the transcriptional repertoire of multicellular organisms.

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