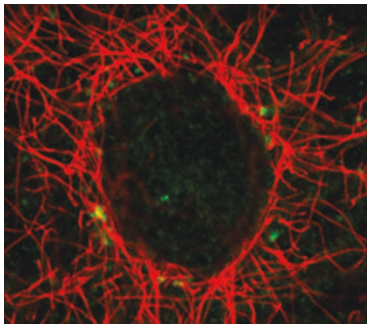
Clipping Frizzled ends



The Wnt protein family is involved in important cell-to-cell communication events during animal development and morphogenesis. Upon secretion, Wnt proteins bind the extracellular domain of members of the Frizzled family of seven–transmembrane domain cell-surface receptors, triggering signaling cascades that can lead to gene transcription. Recent studies suggest a role for the Wnt1 homolog Wingless (Wg) in *Drosophila* synapse development, but how the ligand coordinates differentiation events is unknown. Now, work by Budnik and colleagues examines the effect of Wg signaling on the cellular distribution of its target receptor, DFrizzled 2 (DFz2). The authors show that Wg binding to DFz2 at postsynaptic membranes causes receptor endocytosis. Interestingly, they find that Wg-induced endocytosis results in cleavage of the DFz2 intracellular domain at some point along the endocytic pathway. The cleavage site is at a conserved glutamyl-endopeptidase sequence located adjacent to the final transmembrane domain and generates an 8-kDa fragment. Mutation of the cleavage site reveals that DFz2 cleavage is required for proper synaptic maturation at the neuromuscular junction. Antibody labeling shows that the C-terminal 8-kDa fragment accumulates in the nucleus, where the authors speculate it may participate in regulating gene transcription. These findings indicate the existence of a new mechanism used by Wnt-Frizzled interacting partners to control signaling events that may be specialized to synaptic development. (*Science* **310**, 1344–1347, 2005) *MM*

RNA tether

The processing steps for precursor mRNAs include capping, splicing and 3′ end processing (cleavage and polyadenylation). Many of these different steps are connected to one another and to transcription. The C-terminal domain (CTD) of the largest subunit of RNA polymerase has been suggested to bind the RNA processing factors that interact with the emerging RNA during transcription, physically linking transcription to the processing event. However, the relative importance of this physical link has not been directly addressed. To better understand the coupling of transcription to processing, two groups have examined the effect of severing the RNA tether from the cleavage and polyadenylation site to the RNA polymerase. Martinson and coworkers have developed an *in vitro* system in which transcription is coupled to 3′ end cleavage and polyadenylation. They show that when the RNA tether is cut during transcription, the efficiency of 3′ end processing decreases. They suggest that the nascent RNA and the CTD act together to recruit the processing factors. Bentley and coworkers have studied this problem *in vivo* and show that cleavage of the RNA tether by a ribozyme inhibits 3′ end processing. Further, they show that mutations in the CTD or polyadenylation site inhibit splicing and 3′ end processing, and that splicing can be restored by severing the RNA tether between the polyadenylation site and the polymerase. On the basis of these findings, they suggest that a 3′ cleavage event can enhance splicing of upstream introns by releasing the transcript from the polymerase and allowing it to associate with splicing factors. Thus, under normal processing conditions, a mechanism is in place to prevent full splicing of introns near the 3′ end of the gene until the transcript has been released. Likewise, the observation of coupling between transcription and 3′ end cleavage and polyadenylation suggests that the tether keeps the polyadenylation signal close to the polymerase. Such mechanisms would coordinate the final steps of RNA processing and could serve as important quality controls to assess whether processing should proceed. (*Mol. Cell* **20**, 733–745 and 747–758, 2005) *BK*

Research highlights written by Hwa-ping Feng, Boyana Konforti, Michelle Montoya and Tracy Smith Schmidt.

SMN specificity

Precursor mRNA splicing is mediated by the spliceosome, a large RNA-protein machine. The core of the fully assembled spliceosome consists of five small nuclear ribonucleoprotein particles (snRNPs), each of which contains a different uridine-rich snRNA (U snRNA), a common heptameric Sm protein complex and several snRNP-specific proteins. Sm proteins can assemble promiscuously on uridine-rich RNAs *in vitro*, but biogenesis of U snRNPs requires the survival of motor neurons (SMN) complex, which functions as a specificity factor to ensure that the Sm complex is loaded onto the correct snRNAs. Previous work has defined a consensus RNA sequence ($PuA(U)_{4–6}GPu$, where Pu is a purine) important for U snRNP assembly, known as the Sm site. However, it is not clear whether additional RNA elements contribute to specifying U snRNP assembly. Dreyfuss and colleagues address this issue using viral snRNAs (HSURs), which bind tightly to the SMN complex and can compete with host snRNP assembly. They show that the minimal SMN-binding region of HSURs includes the Sm site and a stem-loop at the 3′ terminus of the RNA. Both features are conserved in most of the U snRNAs. Notably, *in vitro* assembly of the Sm complex on the RNA in the absence of SMN does not require the stem-loop. The stem-loop structure, rather than the actual sequence, is important for SMN binding and Sm assembly. The authors further show that SMN, but not Sm, makes direct contact with the phosphate backbone of the first and the third uridines in the Sm site. Together, these results indicate that SMN recognizes structural features specific to the U snRNAs to facilitate the assembly of the U snRNPs. (*Mol. Cell. Biol.* **25**, 10989–11004, 2005) *HPF*

A new mitotic regulator

During mitosis, separation of sister chromatids is regulated by the anaphase-promoting complex (APC), which has ubiquitin ligase activity. The APC marks certain proteins for destruction, notably cyclin B and securin. Securin binds the protease responsible for cleaving the cohesin complex that holds sister chromatids together. The APC requires an activating subunit, either Cdc20 or Cdh1, and its ubiquitinating activity must be tightly regulated to prevent premature chromatid separation and aneuploidy. van Deursen and colleagues show that two proteins, the mRNA export factor Rae1 and the nucleoporin protein Nup98, form a complex that binds and inhibits Cdh1-activated APC during early mitosis. They use cells derived from single- or double-heterozygous mice with mutations in the *Rae1* or *Nup98* genes to show that both are required to prevent widespread aneuploidy and also that levels of securin are greatly reduced in the doubly mutant cells. Co-immunoprecipitation experiments support a direct interaction between Rae1, Nup98, APC subunits and Cdh1 and show that dissociation of Rae1 and Nup98 from Cdh1-activated APC occurs at the metaphase-to-anaphase transition, when mitotic checkpoint proteins cease to regulate Cdc20-activated APC. Interestingly, however, they find no evidence for an interaction between Rae1, Nup98 and Cdc20. The authors suggest that release of Cdh1-activated APC from the Rae1–Nup98 complex may have a primary role in the destruction of securin. (*Nature* **438**, 1036–1039, 2005) *TSS*