Know thyself

To protect us from infections, the immune system must detect pathogens and trigger the appropriate responses; it must also avoid any reaction against our own healthy tissues. Failure to distinguish 'self' from 'non-self' can result in autoimmune disorders. Recent work has shed light on the development of psoriasis, a common autoimmune skin disease characterized by chronic local inflammation, which is triggered by activated plasmacytoid dendritic cells (pDCs). These cells can detect microbial infections, partly because they express receptors for microbial DNA and RNA, such as TLR9. Structural differences between microbial and mammalian DNA (methylation patterns, for example) contribute to discrimination by these cells, but the subcellular localization of TLR9 is also important in restricting immune responses to foreign nucleic acids. Specifically, TLR9 is found in endosomal and lysosomal compartments, where it can detect DNA or RNA from pathogens such as viruses that invade the cells via endocytosis. By analyzing psoriatic skin extracts, Gilliet and colleagues identified the activating factor for pDCs as LL37, an antimicrobial peptide that protects the skin against bacterial pathogens upon tissue damage. The authors observed that its overproduction can have deleterious consequences. LL37 binds DNA, forming aggregates and condensed structures. LL37-bound DNA can enter pDCs and is retained inside early endosomal compartments, where it interacts with TLR9, activating the cells. Skin damage, known to exacerbate psoriasis, may result in release of dying cells' DNA (self-DNA). This DNA is normally inert, but the high concentrations of LL37 in psoriasis promote detection of self-DNA by pDCs, triggering the inflammatory response that ultimately leads to autoimmunity. These findings show how dysregulation of a component of the immune system can break the barrier between self and non-self. (*Nature*, advance online publication 16 September 2006, doi:10.1038/nature06116) *IC*

Tickling a helicase

Introns are removed from precursor messenger RNAs by two successive transesterification reactions within the spliceosome. DEAD/H-box NTPase enzymes are known to remodel the spliceosome at several steps during the splicing reaction. Once the reaction is complete, the RNA-dependent NTPase Prp43 catalyzes the dissociation of the excised intron in its lariat form. Prp43's ability to hydrolyze ATP is essential for its function; however, it has been unclear how Prp43 couples the energy of ATP hydrolysis to intron release. Schwer and coworkers now show that Ntr1 directly binds Prp43 and stimulates its helicase activity *in vitro*. They conclude that activation by Ntr1 is important for Prp43's biological function, on the basis of two lines of evidence. First, mutations in Prp43 that uncouple ATP hydrolysis from Ntr1-stimulated helicase activity are lethal and prevent lariat-intron release *in vitro*. Such mutations do not affect binding of Prp43 to Ntr1 or to the spliceosome. Second, mutations in Prp43 and Ntr1 that diminish protein-protein interactions, and thus impair stimulation of helicase activity, are detrimental to intron release and cell growth. The authors propose that Ntr1 binds spliceosomes, recruits Prp43 and then activates Prp43's helicase activity to disrupt RNA-RNA or RNA-protein contacts in the spliceosome, dissociating the lariat-intron RNA. What remains to be identified is the molecular target of the helicase activity. (*Genes Dev.* **21**, 2312–2325, 2007) *BK*

Written by Inês Chen, Boyana Konforti, Sabbi Lall & Michelle Montoya

Extracting microRNA mechanisms

MicroRNAs (miRNAs) are small RNAs that bind cognate sequences in their target transcripts. Although it is known that they mediate post-transcriptional repression, the underlying mechanism is controversial. Sonenberg, Duchaine and colleagues have now used a cell extract system to carefully monitor miRNA-mediated repression shortly after application of an *in vitro*–synthesized target transcript at defined concentrations. The authors used mouse Krebs-2 ascites extract, as it recapitulates some defined properties of *in vivo* translation, and assessed repression of a target transcript containing six binding sites for *let-7*, an abundant miRNA in the extract. Control experiments indicated that the system reflects known features of miRNA function. The authors then examined the molecular mechanism, showing that repression requires an intact 5′-methylated cap on the target and can be overcome by adding cap-binding translation initiation factors to the extract. Fewer complexes of reporter RNA with 80S ribosomes were observed within 10 minutes of translation. Subsequently, levels of the target RNA had fallen further than those of the control, suggesting that a rapid translational repression response is later followed, and consolidated, by increased target mRNA turnover. These different responses over time may explain the distinct mechanistic models of miRNA regulation that have emerged. Further work will show whether the insights from this study entirely reflect *in vivo* repression, and whether other aspects of miRNA function, such as the molecular machinery involved, can be dissected using this system. (*Science*, published online 26 July 2007, doi: science.1146067/DC1) *SL*

Motor-free transport

Protein translocation into or across the mitochondrial inner membrane is accomplished by the TIM23 pre-sequence translocase complex. In conjunction with the outer-membrane translocase (TOM) complex, the pre-sequence translocase-associated motor (PAM), and respiratory-chain complexes III and IV, the TIM23 complex transports all mitochondrial pre-proteins with N-terminal pre-sequences. Although TIM23 interactions complex with the TOM and respiratory-chain complexes are short-lived, PAM remains associated with TIM23 both during and after pre-protein translocation. An issue under debate concerns which components of the TIM23 complex are sufficient for membrane integration of pre-proteins bearing a hydrophobic sorting signal. In one scenario, the TIM23 complex exists in two forms: $TIM23^{CORE}$ is responsible for matrix translocation, comprises Tim17, Tim23 and Tim50, and associates with PAM; $TIM23^{SORT}$ controls the release of membrane-destined pre-proteins into the inner membrane and does not associate with PAM, but has an additional subunit, Tim21. In a second scenario, the TIM23 complex exists in a single form that includes Tim21 and PAM and mediates both preprotein translocation and membrane integration. Using genetic and biochemical methods, the Pfanner and Wagner groups have now shown that $TIM23^{SORT}$ exists and can function as a translocase independent of PAM. Further, proteoliposome-reconstituted $TIM23^{SORT}$ was shown to require a membrane potential, such as that generated by the mitochondrial respiratory chain, to efficiently integrate pre-proteins into the membrane. This first successful reconstitution of preprotein insertion will likely pave the way for future studies of protein import machineries. (*Nature Cell Biol.*, advance online publication 9 September 2007, doi:10.1038/ncb1635) *MM*

© 2007 Nature Publishing Group http://www.nature.com/nsmb