Physiology

An end to adolescence

'Puberty' and 'adolescence' are not synonyms, although both terms describe that awkward age between childhood and adulthood. Puberty is defined as the period during which the reproductive system matures. It has a clearly defined marker for when it ends: when bone growth ceases. Adolescence, by contrast, is part physiological, part psychological, part social construct. Chronobiologists joke that people suffer adolescence twice — once themselves, and again when their own children hit the teenage years. But, frustratingly, they have not been able to define precisely when it ends.

Till Roenneberg *et al.* now provide a suitable marker (*Curr. Biol.* **14**, R1038–R1039; 2004). Their questionnaire-based survey of the sleeping habits of 25,000 people between the ages of 10 and 90 confirms the normal distribution of chronotypes in the

population: 'owls', who go to sleep late and wake up late; 'larks', who go to bed early and wake early; and those who fall between the two (the majority of people).

The authors' survey also shows a remarkably robust relationship of this chronotypology to age (see picture). Children are typically early risers but start to sleep

progressively later as they enter adolescence. They reach maximum lateness at around the age of 20, when the curve abruptly starts to decline. The normal distribution of owl-ness and lark-ness in the population is apparent at each age — but, the authors suggest, it is the point at which an individual's curve inverts that marks the end of adolescence.

The data also reflect the earlier development of females compared with males; young women reach their maximum lateness at 19.5 years and young men at 20.9 years. Females tend to be earlier chronotypes than men throughout adulthood, but the gender difference disappears at around 50 — the onset of menopause.

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genomes analysed. The proteins have been proposed to participate in almost every process that involves RNA, including the splicing of precursor mRNAs, the production of the protein-synthesis machinery (ribosomes), mRNA translation, and of course nuclear mRNA export⁷.

Dbp5 was first genetically identified in yeast as a primarily cytoplasmic protein, enriched around the nuclear rim, that is essential for the export of cellular mRNAs from the nucleus^{3,4}. Subsequent analysis⁵ of the human protein revealed a specific association with the cytoplasmic side of nuclear pore complexes (NPCs), the large protein assemblies through which molecules go in and out of the nucleus.

More recently, evidence obtained in insect cells has revealed that Dbp5 actually shuttles between the nucleus and cytoplasm and, at least in part, assembles onto mRNA–protein complexes (mRNPs) as the mRNAs are being synthesized⁹. Importantly, microinjection of frog eggs with a mutant form of Dbp5 that could no longer hydrolyse ATP blocked the export of cellular mRNAs but did not affect mRNA export mediated by HIV-1 Rev and its cellular cofactor Crm1 (ref. 5). Therefore, whereas export of cellular mRNAs by the canonical Tap–Nxt1 pathway depends on Dbp5, the export of very similar viral mRNA substrates through the Rev–Crm1 pathway does not.

This finding suggested two possibilities:

either nuclear export mediated by Rev–Crm1 doesn't require mRNP remodelling, or it depends on a different RNA helicase. The second hypothesis has now been validated by Yedavalli and colleagues⁶. These authors show that overexpressing another member of the DEAD-box family, DDX3, in cultured human cells specifically enhances Rev–Crm1-dependent, but not Tap–Nxt1-dependent, nuclear mRNA export. Inhibiting DDX3 function selectively impairs the former process. Moreover, DDX3 interacts specifically with both Crm1 and Rev *in vivo*. Interestingly, DDX3, like Dbp5, is a nucleocytoplasmic shuttle protein that, at steady state, is predominantly localized at the cytoplasmic face of NPCs. In total, the data indicate that these two helicases, although specific for distinct RNA-export pathways, probably have a similar role in remodelling mRNPs during export (Fig. 1).

So what does DDX3, a cellular enzyme, do in uninfected cells? That remains unclear at present. Although Crm1 is essential for the export of HIV-1 mRNAs, it is not known whether it participates in the export of any cellular mRNAs. It does, however, have a well-established role in exporting proteins — as well as several non-protein-coding RNAs, including ribosomal RNAs¹ — from the nucleus. Yedavalli *et al.* present limited data suggesting that DDX3 is not required for Crm1-mediated protein export. But it might be involved in exporting certain

cellular coding or non-coding RNAs.

This issue is important, because Yedavalli *et al.*⁶ also present convincing evidence that DDX3 has an essential, and possibly rate-limiting, role in the HIV-1 life cycle. Thus they suggest that it might represent a new target for chemotherapeutic intervention. However, as cells undoubtedly did not evolve DDX3 solely for the convenience of this virus, it remains possible that inhibiting it could have unforeseen and harmful consequences. It would therefore seem to be a priority to knock down DDX3 expression in infected and uninfected T cells, the major cell type affected by HIV-1, as an initial test of the hypothesis that this helicase is indeed a worthwhile target for antiviral drug development.

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