SMALL RNAS

A complex discovery

The recent discovery of microRNAs (miRNAs) has caused a great deal of interest, as they appear to be a large group of small RNAs (20–24 nucleotides in length), with an as yet unknown function. But Gideon Dreyfuss and colleagues might have taken the first step towards revealing the purpose of these enigmatic structures with their report in *Genes & Development* of a new class of ribonucleoprotein (RNP) complex that houses several miRNAs.

The main components of the miRNP are Gemin3 and Gemin4 — components of the survival motor neurons (SMN) complex — and the eukaryotic translation initiation factor eIF2C2. The eIF2C2–Gemin3–Gemin4 complex was isolated by immunoprecipitation studies designed to understand the physiological role of Gemin3, a DEAD-box putative RNA helicase. Further analysis of the complex revealed that an RNA pool of around 22 nucleotides could also be precipitated, and that the eIF2C2–Gemin3–Gemin4–miRNA complex sediments at around 15S.

After directionally cloning and sequencing this RNA pool, the authors identified nine miRNAs that had been previously discovered and 31 new miRNAs, which suggests that the number of miRNAs is much higher than previously thought. The sequences of the miRNAs show similarities to another type of small RNA — small temporal RNAs (stRNAs) — which suggests that the miRNAs are derived from larger precursors that have the capacity to form stem–loop structures, and that miRNAs are likely to regulate the expression of other RNAs.

The large number of miRNAs found within the complex suggests that miRNPs recognize a wide range of RNA targets, and identifying these targets will be crucial to understanding the miRNP function. But clues to the pathways and function of miRNAs can also be gained from knowing the functions of Gemin3, Gemin4 and eIF2C2.

The discovery of eIF2C2 — a member of the Argonaute protein family — in the miRNP confirms previous findings that linked these proteins with small RNA function. The presence of Gemin3 and Gemin4 is particularly intriguing as these are also found in the SMN complex, which is a key factor in the biogenesis and function of diverse RNPs. Interestingly, the binding of Gemin3 to the SMN protein (the component from which the name of the SMN complex is derived) is impaired in SMN mutations that are found in patients with spinal muscular atrophy. So, further studies will be required to see what regulates the distribution of Gemin3 and Gemin4 between the SMN complex and miRNPs, and also whether there is a link between miRNPs and progression of this neurological disease.

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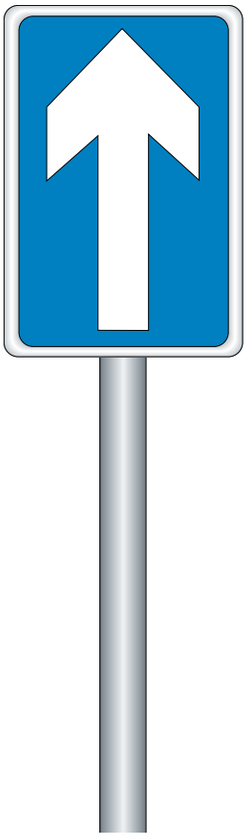
References and links

ORIGINAL RESEARCH PAPER Mourelatos, Z. *et al.* miRNPs: a novel class of ribonucleoproteins containing numerous microRNAs. *Genes Dev.* **16**, 720–728 (2002)



MEMBRANE TRANSPORT

One-way street

Late endocytic compartments (late endosomes and lysosomes) depend on microtubules to move bidirectionally between the cell periphery and perinuclear region. The minus-end-directed motor — cytoplasmic dynein — moves endosomes towards the perinuclear region, whereas the plus-end-directed motor — kinesin — moves them towards the periphery. In *The EMBO Journal*, Gruenberg and colleagues now show that the motility of these compartments depends on their membrane lipid composition and the effect that this composition has on the cycling of the small GTPase Rab7.

The storage disorder Niemann–Pick type C (NPC) is caused by the accumulation of cholesterol in late endocytic compartments, and Gruenberg and co-workers showed that these compartments are essentially immobile in NPC cells. The authors observed the same effect when an antibody against lysobisphosphatidic acid — an unconventional late endosomal lipid — was endocytosed in HeLa cells, a treatment that causes cholesterol to accumulate in late endosomes. They found that the late endocytic compartments in these HeLa cells are paralysed and accumulate in the perinuclear region.

Gruenberg and colleagues found that cholesterol-laden vesicles can still bind to microtubules, but that cholesterol selectively impairs the motility of endosomes. They showed that although cytoplasmic dynein can still direct the movement of cholesterol-laden vesicles towards the perinuclear region, these vesicles seem unable to acquire kinesin activity. The authors therefore concluded that cholesterol-loaded, late endocytic vesicles are translocated by cytoplasmic dynein to the perinuclear region, and that they stay here because they cannot use kinesin.

But what is the molecular basis of this effect? The authors propose that it is probably Rab7 — a GTPase that cycles between a membrane-bound and cytosolic form — that is directing late endocytic compartments down this one-way street. They found that Rab7 overexpression mimics the effects of cholesterol on motility in control cells, and that a Rab7 inhibitory mutant restores the ability of cholesterol-loaded vesicles to move towards the cell periphery.

Gruenberg and co-workers have also shown that cholesterol accumulation both increases the amount of membrane-associated Rab7 and inhibits the extraction of Rab7 from the membrane by a guanine nucleotide dissociation inhibitor. They therefore conclude that membrane lipid composition affects the regulation of the Rab7 cycle and that Rab7, in turn, controls the net movement of late endocytic compartments — a result that has implications for other storage disorders in which cholesterol accumulation occurs.

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References and links

ORIGINAL RESEARCH PAPER Lebrand, C. *et al.* Late endosome motility depends on lipids via the small GTPase Rab7. *EMBO J.* **21**, 1289–1300 (2002)