MACHO found about 15 examples of microlensing in the direction of the LMC — only a fifth of the number needed to account for all the dark matter in the Milky Way, but five times too many to be explained by known populations of stars[7] along the line of sight to the LMC. Frustratingly, most microlensing events yield absolutely no information about the distance to the lens, so it is not known whether it lies close to the source star in the LMC, close to the observer in our Galaxy, or in the vast space in between where we would expect to find MACHOs.

Now the MACHO team[3] have succeeded in directly imaging one of their gravitational microlenses (LMC-5), and positively identify it as a star from the Milky Way. This not only provides a clue to the nature of these lenses, but is also the first successful merger of astrometric and photometric microlensing — a process that will eventually transform the field (see Fig. 1).

The original analysis[8] of light from LMC-5 showed that it contained extra starlight from a faint red star, whose colour and brightness were consistent with it being in the Milky Way, rather than in the LMC, suggesting that this star might be the lens[9]. To test this idea, the MACHO collaboration[3] obtained Hubble images of LMC-5, some six years after the original microlensing measurement. By this time the red star had moved 0.1 arcseconds away from the source, far enough to be seen as a separate object, but close enough to make its identification as the lens virtually certain.

By imaging the lens, the MACHO team have also made the first astrometric microlensing measurement. Because the source and lens were almost coincident at the time of the event, we can calculate their relative angular speed from their positions six years later. Further Hubble observations would allow astronomers to obtain their relative parallax, and so, according to Refsdal's original recipe, the lens mass. (MACHO have already reported[3] a parallax measurement from a photometric observation of LMC-5, but this must still be considered tentative.)

Ultimately, the combination of photometry with astrometry will change the face of microlensing. With nearly microarcsecond precision, NASA's Space Interferometry Mission (SIM) will be able to measure the masses of about a dozen nearby stars with 1% accuracy[10], in just the way that Refsdal originally proposed. But SIM will also combine photometric and astrometric microlensing to measure lens masses by another route, one that can be applied to dark as well as luminous matter. Even though SIM will not be able to see two separate images distorted by the lens, it can effectively determine their separation by tracking the motion of their combined light[11,12]. Because SIM will be in orbit around the Sun, its photometric observations will be affected by parallax relative to those obtained from the Earth (another seminal idea of Refsdal[13]). Combining SIM astrometry with Earth/SIM photometry will then yield the mass, distance and velocity of the lens, even if the lens is completely dark[14].

This idea can be used not only to discover the nature of the lenses detected in the direction of the LMC, but also to measure the masses of a representative sample of all objects, dark and luminous, that inhabit our Milky Way. The OGLE collaboration[15] is detecting hundreds of such lenses in the dense fields of stars found near the centre of the Milky Way, but almost nothing is known about their masses — at least for now. ■

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iCell biology

Conservation signals location

Alexandre Costa and Paul Schedl

During development, many messenger RNAs are spread asymmetrically within cells. Surprisingly, in fruitflies the RNA signals and machinery used for distribution seem to be conserved in different developmental stages.

The asymmetric localization of messenger RNA molecules (mRNAs) is used in cells as diverse as eggs and neurons to restrict the expression and spatial distribution of proteins. mRNA localization depends both on special signals in the mRNAs themselves ('*cis*-acting' signals) and on the RNA-binding proteins that recognize these signals ('*trans*-acting' factors). The resulting RNA–protein complexes in turn interact with machinery that targets the mRNAs to a particular subcellular compartment, where they are ultimately translated into proteins. It has long been assumed that the signals and factors used for localization are unique to the cell type and the mRNA in question. But on page 611 of this issue Bullock and Ish-Horowicz[1] present evidence that, in fruitflies (*Drosophila melanogaster*), the localization of maternal mRNAs during egg development (oogenesis) and of mRNAs expressed during early embryo develop-

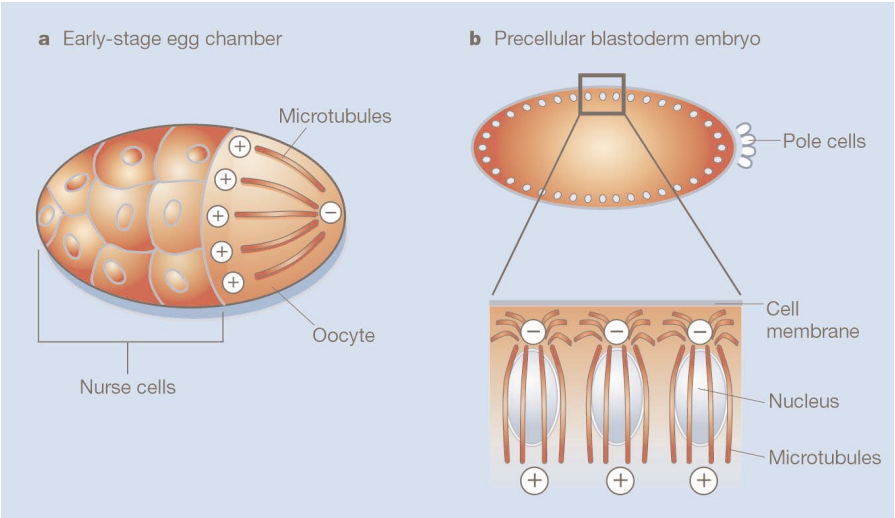

Figure 1 **The asymmetric localization of mRNAs during oocyte and embryo development in *Drosophila*.** a, **An early-stage egg chamber. Several maternal mRNAs, synthesized in the nurse cells, are transported to the developing oocyte and accumulate at the 'minus' end of microtubules.** b, **A precellular blastoderm embryo. Nuclei aligned at the surface of the embryo synthesize pair-rule mRNAs, which accumulate apically after being transported towards the microtubule minus end.**

100 YEARS AGO

For some time past there has been a large and apparently influential party of alarmists with regard to the use of preservatives [in food]. These have all been heard in length by the Committee which has just reported. Their evidence consisted for the most part of elaborate *a priori* argument, in support of which the most profound erudition was occasionally produced; but, as the report politely says, the opinion expressed was not always based directly on fact. In fact, if an inquirer turns the 500 pages of the Blue-book over in search of unequivocal instances of injury to health from preservatives or, indeed, colouring matters in food he will be lucky if he finds a single one… Upon such data it is obvious that the prohibition of preservatives *en masse* was out of the question, and the recommendations of the Committee practically resolve themselves into the regulation and control rather than the prohibition of preservatives. There are, however, two exceptions to this; formaline or formic aldehyde is prohibited altogether, and all preservatives and colouring matters are prohibited in milk.

From *Nature* 5 December 1901.

50 YEARS AGO

It has been suggested by Kistiakovsky that the mechanism of smell could be explained by the existence in the olfactory mucosa of four enzyme groups… and that odoriferous substances are distinguished by their differential inhibition of particular enzyme groups. The same explanation might be used to account for a mechanism capable of distinguishing between substances of different taste… we suggest the following tentative hypothesis to explain [the enzymes'] relation to the mechanism of taste. The chemical reaction involved in the breakdown of substrate by enzyme presumably gives rise to ionic changes which would induce currents in nearby nerve fibres… A tasting substance coming into contact with superficial enzyme sites… would inhibit the activity of an enzyme in one site, accelerate the activity of an enzyme in another site and have no effect on enzymes in other sites and so on. It would therefore alter the pattern of nerve impulses reaching the brain, and each substance would produce its own individual pattern. Since there are six main sites of enzyme activity… we have a mechanism for distinguishing between 2,160 tasting substances.

From *Nature* 8 December 1951.

ment depends on common signals and factors.

Asymmetric mRNA localization is crucial in establishing polarity in developing *Drosophila* eggs and early embryos. During egg (oocyte) development, mRNAs expressed in a cluster of interconnected auxiliary cells (nurse cells) are first transported into the oocyte and then targeted to specific locations within the oocyte (Fig. 1a). Once there, some of these maternal mRNAs are translated more or less immediately; their protein products help to lay down the oocyte's two 'polarity axes' (anterior–posterior and dorsal–ventral). Other localized maternal mRNAs, such as *bicoid*, are translated in the early embryo rather than the oocyte, producing a gradient of bicoid protein. This gradient helps to establish embryonic polarity by directing the initial expression of embryonic patterning genes in 'precellular blastoderm embryos' — an early stage of development in which thousands of cell nuclei are distributed around the surface of the embryo and share a common cytoplasm (Fig. 1b).

The first such patterning genes to be expressed are the gap genes, and their products form short-range gradients that subdivide the embryo into broad domains. The gap mRNAs are distributed uniformly in the cytoplasm at the surface of the embryo, and this is thought to facilitate the formation of short-range gradients extending across several nuclei[2]. The gap proteins in turn control the expression of the pair-rule genes, which further subdivide the embryo. In contrast with the unlocalized gap mRNAs, pair-rule mRNAs are targeted apically, that is, to the cytoplasm just above the nuclei that express the mRNAs[3]. This decreases the lateral diffusion of the encoded proteins, helping to refine the pattern of pair-rule gene expression and to promote the subdivision of the embryo into segments once cells have formed.

There are hints that some of the steps involved in localizing maternal mRNAs in oocytes and pair-rule mRNAs in early embryos depend on common mechanisms. First, an analysis of mRNA localization in early embryos that lack large sections of their genetic material indicated that the *trans*-acting factors required for apical localization must be maternally derived rather than expressed in the embryo[4]. Second, pair-rule mRNAs are transported to the apical cytoplasm along tracks known as microtubules, by motor proteins that move towards the 'minus' end of microtubules[5]. Similarly, the localization of several maternal mRNAs in oocytes depends on microtubules, and accumulation is directed towards the minus end[6].

Bullock and Ish-Horowicz[1] test the idea directly by investigating whether the localization machinery in blastoderm embryos can target maternal mRNAs (rather than the usual pair-rule mRNAs) to an apical location. They find that maternal messages such as *K10*, *gurken*, *bicoid*, *oskar* and *nanos* are recognized by the embryonic machinery and localized preferentially to the apical cytoplasm. Conversely, pair-rule mRNAs that are expressed artificially during oogenesis accumulate in the oocyte in a pattern resembling that of *K10* and several other maternal mRNAs.

Two other lines of evidence indicate that at least some of the same *trans*-acting factors must be used during oogenesis and embryo development. The first comes from the authors' studies[1] of two proteins, Bicaudal D and Egalitarian, which are required for mRNA localization during egg development and form a complex that accumulates at the minus ends of microtubules in oocytes[7,8]. Bullock and Ish-Horowicz[1] find that these proteins are also enriched apically in embryos and localize with a component of a minus-end-directed motor protein, dynein. Moreover, both proteins are required for the apical localization of pair-rule (naturally expressed) and maternal (artificially expressed) mRNAs in early embryos.

Second, Bullock and Ish-Horowicz[1] studied *cis*-acting localization signals. They show that the shortest RNA signal known to be active during egg development, the *K10TLS*, can also target normally unlocalized mRNAs to an apical location in embryos. This RNA signal is predicted to fold into a shape known as a 'stem–loop' structure. Mutations that disrupt this structure block the localization of *K10* during egg development; compensatory mutations that restore the structure also restore localization[9]. Bullock and Ish-Horowicz[1] find that these disrupting and compensatory mutations have the same effects on mRNA targeting in embryos, arguing that the factors that recognize the stem–loop in eggs are likely to be present in embryos, too. Conversely, pair-rule transcripts that lack the minimum apical-localization element fail to accumulate in the oocyte when expressed during oogenesis.

The simplest explanation is that the same signals and factors are used to recognize and localize different mRNAs in different developmental contexts. If true, one might expect that mRNAs that show similar localization patterns in oocytes or embryos would have similar signals. Indeed, the *orb* mRNA, which is localized similarly to *K10* in oocytes, contains a localization element that is closely related in sequence and structure to the *K10TLS*[9]. Moreover, a 150-nucleotide element involved in targeting *oskar* mRNA during oogenesis[10] has a stem–loop structure resembling that in the *K10TLS*, and the *K10TLS* can substitute for this element[9].

However, *orb* (and *oskar*) may be the exception rather than the rule: the localiza-