

# When the Swiss clock goes wrong

## Regulation of Aurora A by UBXN-2/CDC-48

Elsa Kress<sup>1,\*</sup> and Monica Gotta<sup>2</sup>

<sup>1</sup>Centre de Génétique et Physiologie Moléculaire et Cellulaire; Université Lyon 1; Lyon, France; <sup>2</sup>Département de Physiologie Cellulaire et Métabolisme; Centre Médico-Universitaire; Université de Genève; Geneva, Switzerland

A Swiss clock and entry into mitosis have something in common: both must be very precise. When the Swiss clock goes wrong, the consequence is the loss of reputation. When entry into mitosis goes wrong, cells may divide in an aberrant way. More generally, cell division events are tightly regulated at the temporal and spatial levels.<sup>1</sup> We have recently shown that in *C. elegans*, misregulation of the timing of centrosome maturation can result in spindle orientation defects and in aberrant asymmetric cell division.<sup>2</sup>

During asymmetric cell division the mitotic spindle aligns along the polarity axis, so that cell fate determinants are properly segregated to the daughter cells.<sup>1</sup> In the *C. elegans* one-cell embryo, polarity is established shortly after fertilization. The centrosomes, future poles of the mitotic spindle, are first aligned perpendicularly to the polarity axis and re-orient during prophase (Fig. 1A). The highly dynamic properties of astral microtubules and their contacts with the cortex contribute to the reorientation. To be able to generate long and dynamic astral microtubules, the centrosomes must undergo maturation, a process that allows accumulation of proteins essential for centrosomal function (pericentriolar material, PCM). Centrosome maturation starts with accumulation of the cell cycle kinase Aurora A and goes on with the progressive Aurora A-dependent recruitment of regulators of astral microtubule number, length, and dynamics.<sup>3</sup>

To our knowledge, our work is the first evidence that precocious centrosome maturation causes spindle mis-orientation and is therefore deleterious for *C. elegans* asymmetric division.<sup>2</sup> We show that UBXN-2,

the substrate adaptor of the AAA ATPase CDC-48/p97, slows down the recruitment to centrosomes of Aurora A at the onset of mitosis, thus coordinating their maturation with other mitotic events and allowing correct positioning of the mitotic spindle. When this regulation is abolished by depletion of UBXN-2, the centrosomes mature precociously and produce, already in early prophase, long astral microtubules whose dynamics are comparable to those observed in metaphase in wild-type embryos. Those microtubules make too many and/or too strong contacts with the cell cortex and prevent alignment of the mitotic spindle with the polarity axis. The cell therefore divides with the wrong axis, and the embryo dies during development (Fig. 1C).

The role of CDC-48/p97 substrate adaptors is to recognize “labeled” proteins, extract them from complexes or subcellular structures, and send them to degradation or recycling (Fig. 1B). This is one way for a cell to regulate in space and time the localization of key regulatory factors and achieve coordination of cell cycle events.<sup>4</sup> UBXN-2 promotes the removal of AIR-1 from centrosomes specifically during prophase, as in metaphase AIR-1 centrosomal levels are the same in wild-type and UBXN-2-depleted embryos. We speculate that at this cell cycle stage, UBXN-2 is able to recognize AIR-1, thus recruiting CDC-48 and allowing the extraction of AIR-1 from the PCM (Fig. 1B). This hypothesis is supported by our observation that UBXN-2 is enriched around centrosomes during prophase and after metaphase. It is still unclear how UBXN-2 recognizes AIR-1 and how this process is regulated in time.

UBXN-2 lacks the Ubiquitin binding domain found in many CDC-48 cofactors, suggesting that AIR-1 ubiquitination is not involved. Other modifications may be involved, or UBXN-2 has a yet-unrecognized Ubiquitin binding domain. The precise timing of extraction from centrosomes may be regulated by the timing of such modification(s) and/or by regulation of UBXN-2. UBXN-2 is indeed a phosphoprotein, although the kinase that phosphorylates it is still unknown in *C. elegans*. UBXN-2 is enriched around centrosomes also in late mitosis, where its role could again be to remove AIR-1 in preparation for the next cell cycle.

This regulation of Aurora A centrosomal levels is conserved in human cells. Depletion of the orthologs of UBXN-2, p37/p47, results in an increase of Aurora A levels at centrosome during early prophase and in a spindle orientation defects in HeLa cells. However, our data suggest that the spindle orientation defect is not a consequence of the increased centrosomal Aurora A levels. We find that increased centrosomal Aurora A levels delay centrosome separation (Fig. 1C), and this phenotype does not correlate with the spindle orientation defect. How increased Aurora A affects centrosome separation and how p37 and p47 regulate mitotic spindle orientation is as yet not known.

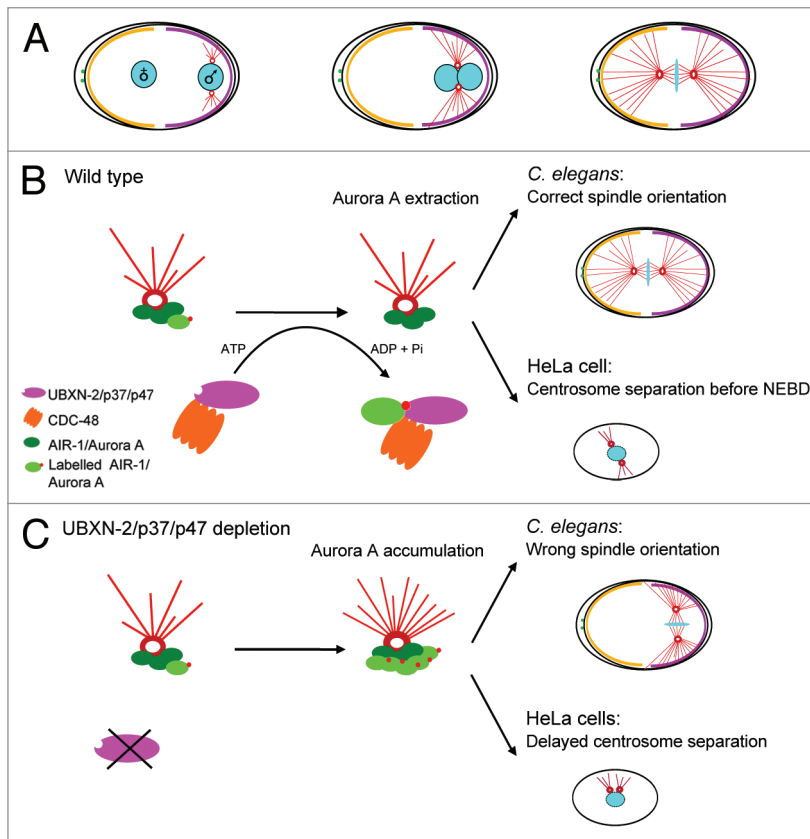
Our work describes a new and conserved role of CDC-48 and its cofactor UBXN-2 in coordinating events at the onset of mitosis. We show how Aurora A recruitment at centrosomes needs to be slowed down to prevent their precocious maturation, and provide the first evidence of its deleterious effect on asymmetrically dividing cells.

\*Correspondence to: Elsa Kress; Email: elsa.kress@univ-lyon1.fr

Submitted: 06/17/13; Accepted: 06/20/13

<http://dx.doi.org/10.4161/cc.26177>

Comment on: Kress E, et al. *J Cell Biol* 2013; 201:559-75; PMID:23649807; <http://dx.doi.org/10.1083/jcb.201209107>



**Figure 1.** (A) Schematic drawing of the dividing *C. elegans* one-cell embryo. Left: In wild-type embryos (represented as an ellipsoid), cell-fate determinants (orange and purple arc) are segregated to the 2 poles of the embryo during early prophase. Middle: after female pronucleus migration (DNA in blue), the centrosomes (red circles) are oriented perpendicularly with the polarity axis. Right: The centrosomes/pronuclei complex rotates of 90° before spindle formation. From the beginning of division, centrosomes produce an increase number of microtubules long enough to reach the cortex (red lines). Proposed mechanisms of the action of UBXN-2/p37/p47 on AIR-1/Aurora A. (B) A pool of AIR-1/Aurora A at centrosomes (light green) is labeled (red dot) and recognized by UBXN-2/p37/p47 and CDC-48. The energy of ATP hydrolysis is used to segregate AIR-1/Aurora A from centrosome and send it to degradation or recycling. Centrosome maturation timing is coordinated with the cell cycle: the spindle orients in the *C. elegans* embryo, and centrosomes separate before NEBD (represented by the dotted line) in HeLa cells. (C) In absence of UBXN-2 or p37/p47, the centrosomes accumulate AIR-1/Aurora A. In *C. elegans*, centrosomes produce more astral microtubules, which lead to spindle misorientation defects. In human cells, centrosome separation is delayed.

## References

1. Morin X, et al. Dev Cell 2011; 21:102-19; PMID:21763612; <http://dx.doi.org/10.1016/j.devcel.2011.06.012>
2. Kress E, et al. J Cell Biol 2013; 201:559-75; PMID:23649807; <http://dx.doi.org/10.1083/jcb.201209107>
3. Barr AR, et al. J Cell Sci 2007; 120:2987-96; PMID:17715155; <http://dx.doi.org/10.1242/jcs.013136>
4. Meyer H, et al. Biochem Soc Trans 2008; 36:126-30; PMID:18208399; <http://dx.doi.org/10.1042/BST0360126>