

Year of publication 2017

Jordan W Raff, Renata Basto (2017 Feb 8)

Centrosome Amplification and Cancer: A Question of Sufficiency.

Developmental cell : 217-218 : [DOI : S1534-5807\(17\)30036-9](https://doi.org/10.1016/j.devcel.2017.02.009)

Summary

Centrosome amplification is a common feature of many types of cancer, but whether it is a cause or consequence is hotly debated. In this issue of *Developmental Cell*, Levine et al. (2017) provide strong evidence that centrosome amplification is sufficient to initiate tumorigenesis in a mouse model.

Year of publication 2015

Maddalena Nano, Renata Basto (2015 Dec 9)

The Janus soul of centrosomes: a paradoxical role in disease?

Chromosome research : an international journal on the molecular, supramolecular and evolutionary aspects of chromosome biology : 127-44 : [DOI : 10.1007/s10577-015-9507-3](https://doi.org/10.1007/s10577-015-9507-3)

Summary

The centrosome is the main microtubule organizing center of animal cells. It contributes to spindle assembly and orientation during mitosis and to ciliogenesis in interphase. Numerical and structural defects in this organelle are known to be associated with developmental disorders such as dwarfism and microcephaly, but only recently, the molecular mechanisms linking centrosome aberrations to altered physiology are being elucidated. Defects in centrosome number or structure have also been described in cancer. These opposite clinical outcomes-arising from reduced proliferation and overproliferation respectively-can be explained in light of the tissue- and developmental-specific requirements for centrosome functions. The pathological outcomes of centrosome deficiencies have become clearer when considering its consequences. Among them, there are genetic instability (mainly aneuploidy, a defect in chromosome number), defects in the symmetry of cell division (important for cell fate specification and tissue architecture) and impaired ciliogenesis. In this review, we discuss the origins and the consequences of centrosome flaws, with particular attention on how they contribute to developmental diseases.

Delphine Gogendeau, Katarzyna Siudeja, Davide Gambarotto, Carole Pennetier, Allison J Bardin, Renata Basto (2015 Nov 17)

Aneuploidy causes premature differentiation of neural and intestinal stem cells.

Nature communications : 8894 : [DOI : 10.1038/ncomms9894](https://doi.org/10.1038/ncomms9894)

Summary

Aneuploidy is associated with a variety of diseases such as cancer and microcephaly.

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Although many studies have addressed the consequences of a non-euploid genome in cells, little is known about their overall consequences in tissue and organism development. Here we use two different mutant conditions to address the consequences of aneuploidy during tissue development and homeostasis in *Drosophila*. We show that aneuploidy causes brain size reduction due to a decrease in the number of proliferative neural stem cells (NSCs), but not through apoptosis. Instead, aneuploid NSCs present an extended G1 phase, which leads to cell cycle exit and premature differentiation. Moreover, we show that this response to aneuploidy is also present in adult intestinal stem cells but not in the wing disc. Our work highlights a neural and intestine stem cell-specific response to aneuploidy, which prevents their proliferation and expansion.

Renata Basto, Karen Oegema (2015 Sep 18)

Methods in Cell Biology. Centrosome & Centriole. Preface.

Methods in cell biology : xvii-xix

Summary

Özdemirhan Serçin, Jean-Christophe Larsimont, Andrea E Karambelas, Veronique Marthiens, Virginie Moers, Bram Boeckx, Marie Le Mercier, Diether Lambrechts, Renata Basto, Cédric Blanpain (2015 Jun 22)

Transient PLK4 overexpression accelerates tumorigenesis in p53-deficient epidermis.

Nature cell biology : 100-10 : [DOI : 10.1038/ncb3270](https://doi.org/10.1038/ncb3270)

Summary

Aneuploidy is found in most solid tumours, but it remains unclear whether it is the cause or the consequence of tumorigenesis. Using Plk4 overexpression (PLK4OE) during epidermal development, we assess the impact of centrosome amplification and aneuploidy on skin development and tumorigenesis. PLK4OE in the developing epidermis induced centrosome amplification and multipolar divisions, leading to p53 stabilization and apoptosis of epidermal progenitors. The resulting delayed epidermal stratification led to skin barrier defects. Plk4 transgene expression was shut down postnatally in the surviving mice and PLK4OE mice never developed skin tumours. Concomitant PLK4OE and p53 deletion (PLK4OE/p53cKO) rescued the differentiation defects, but did not prevent the apoptosis of PLK4OE cells. Remarkably, the short-term presence of cells with supernumerary centrosomes in PLK4OE/p53cKO mice was sufficient to generate aneuploidy in the adult epidermis and triggered spontaneous skin cancers with complete penetrance. These results reveal that aneuploidy induced by transient centrosome amplification can accelerate tumorigenesis in p53-deficient cells.

Renata Basto, Wallace F Marshall (2015 May 28)

Methods in cilia & flagella. Preface.

Methods in cell biology : xxi-xxii

Summary

Maria A Rujano, Renata Basto, Véronique Marthiens (2015 May 27)

New insights into centrosome imaging in *Drosophila* and mouse neuroepithelial tissues.

Methods in cell biology : 211-27 : [DOI : 10.1016/bs.mcb.2015.04.005](https://doi.org/10.1016/bs.mcb.2015.04.005)

Summary

The centrosome is the main microtubule-organizing center in animal cells. It participates in the assembly of a bipolar spindle that ensures accurate segregation of chromosomes during mitosis. Recently, mutations in centrosome genes have been identified in patients affected by neurodevelopmental disorders. In fact, the etiology of several neurodevelopmental pathologies seems to be linked to defects in the assembly of the mitotic spindle in the neural stem cell compartment during neurogenesis. Therefore, getting better insights into the structure and function/dysfunction of the mitotic spindle apparatus in an intact tissue environment is of utmost importance. However, imaging nanometer-scale structures like centrosomes and microtubule bundles within the depth of a tissue is still challenging. Here we describe two procedures to acquire high-resolution images on fixed tissues and to perform live imaging of microtubule-based structures in the neuroepithelia of the *Drosophila* brain and of the mouse neocortex. We take advantage of the accumulation of centrosomes and mitotic figures at the apical surface of these polarized tissues to improve the quality of staining and imaging. Both *Drosophila* and mouse models with centrosome dysfunction showed abnormalities in the neuroepithelium reminiscent of the ones described in brains of human patients. These observations have highlighted their value as model organisms to study the etiology of human neurodevelopmental pathologies.

Teresa Mendes Maia, Perrine Paul-Gilloteaux, Renata Basto (2015 Feb 14)

Quantitative analysis of flagellar proteins in *Drosophila* sperm tails.

Methods in cell biology : 263-78 : [DOI : 10.1016/bs.mcb.2015.01.003](https://doi.org/10.1016/bs.mcb.2015.01.003)

Summary

The cilium has a well-defined structure, which can still accommodate some morphological and molecular composition diversity to suit the functional requirements of different cell types. The sperm flagellum of the fruit fly *Drosophila melanogaster* appears as a good model to study the genetic regulation of axoneme assembly and motility, due to the wealth of genetic tools publically available for this organism. In addition, the fruit fly's sperm flagellum displays quite a long axoneme (~1.8mm), which may facilitate both histological and biochemical analyses. Here, we present a protocol for imaging and quantitatively analyze proteins, which associate with the fly differentiating, and mature sperm flagella. We will use

as an example the quantification of tubulin polyglycylation in wild-type testes and in Bug22 mutant testes, which present defects in the deposition of this posttranslational modification. During sperm biogenesis, flagella appear tightly bundled, which makes it more challenging to get accurate measurements of protein levels from immunostained specimens. The method we present is based on the use of a novel semiautomated, macro installed in the image processing software ImageJ. It allows to measure fluorescence levels in closely associated sperm tails, through an exact distinction between positive and background signals, and provides background-corrected pixel intensity values that can directly be used for data analysis.

Year of publication 2014

Dora Sabino, Delphine Gogendeau, Davide Gambarotto, Maddalena Nano, Carole Pennetier, Florent Dingli, Guillaume Arras, Damarys Loew, Renata Basto (2014 Sep 23)

Moesin is a major regulator of centrosome behavior in epithelial cells with extra centrosomes.

Current biology : CB : 879-89 : [DOI : 10.1016/j.cub.2015.01.066](https://doi.org/10.1016/j.cub.2015.01.066)

Summary

Centrosome amplification has severe consequences during development and is thought to contribute to a variety of diseases such as cancer and microcephaly. However, the adverse effects of centrosome amplification in epithelia are still not known. Here, we investigate the consequences of centrosome amplification in the *Drosophila* wing disc epithelium. We found that epithelial cells exhibit mechanisms of clustering but also inactivation of extra centrosomes. Importantly, these mechanisms are not fully efficient, and both aneuploidy and cell death can be detected. Epithelial cells with extra centrosomes generate tumors when transplanted into WT hosts and inhibition of cell death results in tissue over-growth and disorganization. Using SILAC-fly, we found that Moesin, a FERM domain protein, is specifically upregulated in wing discs with extra centrosomes. Moesin localizes to the centrosomes and mitotic spindle during mitosis, and we show that Moesin upregulation influences extra-centrosome behavior and robust bipolar spindle formation. This study provides a mechanistic explanation for the increased aneuploidy and transformation potential primed by centrosome amplification in epithelial tissues.

Charlotte Mariani, Marion Desdouits, Cyril Favard, Philippe Benaroch, Delphine M Muriaux (2014 Jul 11)

Role of Gag and lipids during HIV-1 assembly in CD4(+) T cells and macrophages.

Frontiers in microbiology : 312 : [DOI : 10.3389/fmicb.2014.00312](https://doi.org/10.3389/fmicb.2014.00312)

Summary

HIV-1 is an RNA enveloped virus that preferentially infects CD4(+) T lymphocytes and also

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macrophages. In CD4(+) T cells, HIV-1 mainly buds from the host cell plasma membrane. The viral Gag polyprotein targets the plasma membrane and is the orchestrator of the HIV assembly as its expression is sufficient to promote the formation of virus-like particles carrying a lipidic envelope derived from the host cell membrane. Certain lipids are enriched in the viral membrane and are thought to play a key role in the assembly process and the envelop composition. A large body of work performed on infected CD4(+) T cells has provided important knowledge about the assembly process and the membrane virus lipid composition. While HIV assembly and budding in macrophages is thought to follow the same general Gag-driven mechanism as in T-lymphocytes, the HIV cycle in macrophage exhibits specific features. In these cells, new virions bud from the limiting membrane of seemingly intracellular compartments, where they accumulate while remaining infectious. These structures are now often referred to as Virus Containing Compartments (VCCs). Recent studies suggest that VCCs represent intracellularly sequestered regions of the plasma membrane, but their precise nature remains elusive. The proteomic and lipidomic characterization of virions produced by T cells or macrophages has highlighted the similarity between their composition and that of the plasma membrane of producer cells, as well as their enrichment in acidic lipids, some components of raft lipids and in tetraspanin-enriched microdomains. It is likely that Gag promotes the coalescence of these components into an assembly platform from which viral budding takes place. How Gag exactly interacts with membrane lipids and what are the mechanisms involved in the interaction between the different membrane nanodomains within the assembly platform remains unclear. Here we review recent literature regarding the role of Gag and lipids on HIV-1 assembly in CD4(+) T cells and macrophages.

Véronique Marthiens, Renata Basto (2014 Feb 24)

[From centrosomes to microcephaly: follow the link].

Médecine sciences : M/S : 133-6 : [DOI : 10.1051/medsci/20143002006](https://doi.org/10.1051/medsci/20143002006)

Summary

Véronique Marthiens, Renata Basto (2014 Feb 22)

Microcephaly: STIL(I) a tale of too many centrosomes.

Current biology : CB : R162-4 : [DOI : 10.1016/j.cub.2013.12.054](https://doi.org/10.1016/j.cub.2013.12.054)

Summary

Centrosome mutations associated with microcephaly are normally thought to result in loss-of-function phenotypes. A new study shows, however, that mutations found in the human microcephaly STIL gene cause centrosome amplification, suggesting a direct link between the presence of extra centrosomes and the establishment of this disease.

Teresa Mendes Maia, Delphine Gogendeau, Carole Pannetier, Carsten Janke, Renata Basto (2014 Feb 15)

Bug22 influences cilium morphology and the post-translational modification of ciliary microtubules.

Biology open : 138-51 : [DOI : 10.1242/bio.20146577](https://doi.org/10.1242/bio.20146577)

Summary

Cilia and flagella are organelles essential for motility and sensing of environmental stimuli. Depending on the cell type, cilia acquire a defined set of functions and, accordingly, are built with an appropriate length and molecular composition. Several ciliary proteins display a high degree of conservation throughout evolution and mutations in ciliary genes are associated with various diseases such as ciliopathies and infertility. Here, we describe the role of the highly conserved ciliary protein, Bug22, in *Drosophila*. Previous studies in unicellular organisms have shown that Bug22 is required for proper cilia function, but its exact role in ciliogenesis has not been investigated yet. Null Bug22 mutant flies display cilia-associated phenotypes and nervous system defects. Furthermore, sperm differentiation is blocked at the individualization stage, due to impaired migration of the individualization machinery. Tubulin post-translational modifications (PTMs) such as polyglycylation, polyglutamylolation or acetylation, are determinants of microtubule (MT) functions and stability in centrioles, cilia and neurons. We found defects in the timely incorporation of polyglycylation in sperm axonemal MTs of Bug22 mutants. In addition, we found that depletion of human Bug22 in RPE1 cells resulted in the appearance of longer cilia and reduced axonemal polyglutamylolation. Our work identifies Bug22 as a protein that plays a conserved role in the regulation of PTMs of the ciliary axoneme.

Year of publication 2013

Maria A Rujano, Luis Sanchez-Pulido, Carole Pannetier, Gaelle le Dez, Renata Basto (2013 Feb 6)

The microcephaly protein Asp regulates neuroepithelium morphogenesis by controlling the spatial distribution of myosin II.

Nature cell biology : 1294-306 : [DOI : 10.1038/ncb2858](https://doi.org/10.1038/ncb2858)

Summary

Mutations in ASPM are the most frequent cause of microcephaly, a disorder characterized by reduced brain size at birth. ASPM is recognized as a major regulator of brain size, yet its role during neural development remains poorly understood. Moreover, the role of ASPM proteins in invertebrate brain morphogenesis has never been investigated. Here, we characterized the function of the *Drosophila* ASPM orthologue, Asp, and found that asp mutants present severe defects in brain size and neuroepithelium morphogenesis. We show that size reduction depends on the mitotic function of Asp, whereas regulation of tissue shape depends on an uncharacterized function. Asp interacts with myosin II regulating its polarized distribution along the apico-basal axis. In the absence of Asp, mislocalization of myosin II results in interkinetic nuclear migration and tissue architecture defects. We propose that Asp regulates neuroepithelium morphogenesis through myosin-II-mediated structural and mechanical processes to maintain force balance and tissue cohesiveness.

Year of publication 2012

Véronique Marthiens, Maria A Rujano, Carole Pernetier, Sarah Tessier, Perrine Paul-Gilloteaux, Renata Basto (2012 Nov 15)

Centrosome amplification causes microcephaly.

Nature cell biology : 731-40 : [DOI : 10.1038/ncb2746](https://doi.org/10.1038/ncb2746)

Summary

Centrosome amplification is a hallmark of human tumours. In flies, extra centrosomes cause spindle position defects that result in the expansion of the neural stem cell (NSC) pool and consequently in tumour formation. Here we investigated the consequences of centrosome amplification during mouse brain development and homeostasis. We show that centrosome amplification causes microcephaly due to inefficient clustering mechanisms, where NSCs divide in a multipolar fashion producing aneuploid cells that enter apoptosis. Importantly, we show that apoptosis inhibition causes the accumulation of highly aneuploid cells that lose their proliferative capacity and differentiate, thus depleting the pool of progenitors. Even if these conditions are not sufficient to halt brain development, they cause premature death due to tissue degeneration. Our results support an alternative concept to explain the etiology of microcephaly and show that centrosome amplification and aneuploidy can result in tissue degeneration rather than overproliferation and cancer.