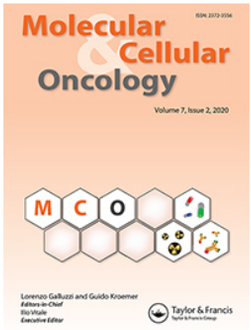

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COMMENTARY

Doryphagy: when selective autophagy safeguards centrosome integrity

Valentina Cianfanelli [a] and Francesco Cecconi [a,b,c]

[a]Unit of Cell Stress and Survival, Center for Autophagy, Recycling and Disease (CARD), Danish Cancer Society Research Center, Copenhagen, Denmark; [b]Department of Pediatric Hemato-Oncology and Cell and Gene Therapy, IRCCS Bambino Gesù Children's Hospital, Rome, Italy; [c]Department of Biology, University of Rome Tor Vergata, Rome, Italy

ABSTRACT

Although centrosome abnormalities are frequent in cancer, the mechanisms responsible for their accumulation are poorly understood. Here we comment on our recent publication identifying a new type of selective autophagy, named doryphagy, which preserves centrosome organization through targeting Centriolar Satellites (CS). Thus, doryphagy prevents inaccurate mitosis and genomic instability.

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The Centriolar Satellites (CS) are non-membranous organelles moving along the microtubules, toward the centrosome. By this movement, CS shuttle centrosomal proteins at the centrosome, regulating its assembly and dynamics. Consistently, CS are highly enriched for centrosomal proteins, which are gathered around the CS master organizer, the scaffold protein pericentriolar material 1 (PCM1).[1] Although PCM1 is required for CS assembly, mechanisms taking care of CS homeostasis and turnover were mostly unknown, till very recently.

Autophagy is a catabolic process recycling cellular components and damaged organelles. It involves the sequestration of cellular material in double-membrane vesicles, the autophagosomes, which fuse with lysosomes, where the engulfed material is degraded.[2] While autophagy was originally considered a nonselective process, it has now been established that it displays selectivity in many contexts. Indeed, autophagy can specifically recruit organelles and protein complexes for autophagic degradation, by means of autophagy adapters and/or receptors.[3]

In our recent publication, we characterize a novel type of selective autophagy that targets the CS, and that we named doryphagy (from the Greek word "doryphoros", for satellites).[4] This selective disposal of CS relies on the direct interaction between PCM1 and the autophagy receptors GABARAP/GABARAPL2 (GABARAPs), mediated by LIR (LC3 Interacting Region) motifs. This interaction drives the engulfment of CS into autophagosomes, where they are eventually degraded by lysosomal enzymes. Doryphagy occurs already in basal condition, keeping CS level in check, but is also further enhanced upon autophagy induction (e.g. upon starvation or mTOR inhibition). Because CS regulate centrosome homeostasis, autophagy/doryphagy disruption results in the accumulation of centrosome abnormalities, which cause inaccurate mitosis and chromosomal aberrations[5] (Figure 1).

Signaling events tightly regulate the timing and dynamics of substrate targeting by selective autophagy:[3] most likely, dorypahgy is no exception. When an autophagy receptor binds an LIR-containing protein – as GABARAPs bind PCM1 during doryphagy -, there must exist ways to hide/expose the LIR motif in a regulated fashion, in order to modulate the affinity for the receptor and prevent unwanted degradation. While how doryphagy is regulated is unknown at the moment, the mechanisms identified so far for other kinds of selective autophagy include stimulatory and inhibitory phosphorylations of residues near/in the LIR motif.[3] Also, post-translational modifications of proteins sitting on the cargo, but not necessarily binding the receptor, can play a role in cargo degradation. If this regulatory model also applies to doryphagy, the PCM1/CEP131 kinase – Polo-Like Kinase 4 (PLK4) – may be a good candidate for the job.[6] Note that identifying the molecular events that govern doryphagy would expand our knowledge about the mechanisms causing centrosome abnormalities. In addition, the identified regulatory molecules could be targeted to counteract the accumulation of centrosome abnormalities in several pathological conditions, including cancer.

Inaccurate mitosis is a major cause of genomic instability. Therefore, it was not surprising to us that autophagy/doryphagy depletion also results in chromosome segregation defects and accumulation of micronuclei. However, most autophagy-deficient cells survive abnormal cell division.[5] This supports the hypothesis that autophagy-deficient cancers may be close to the threshold of tolerance for mitotic defects, hence could be particularly vulnerable to chemotherapeutics targeting mitosis. In that case, coupling autophagy- and mitosis-targeting drugs should be considered as a clinical strategy. At the same time, it may be relevant to assess if autophagy/doryphagy levels can predict cancer sensitivity to mitosis-targeting drugs.

CONTACT Valentina Cianfanelli valecia@cancer.dk; Francesco Cecconi cecconi@cancer.dk

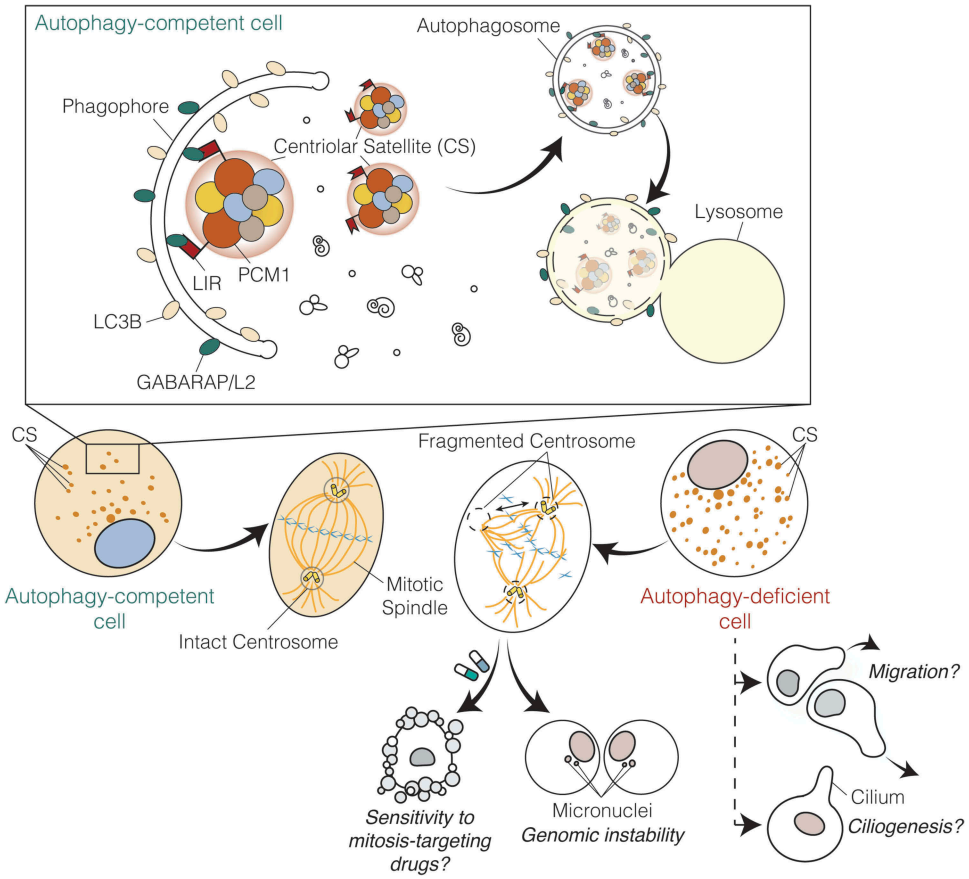

Figure 1. Doryphagy: selective degradation of centriolar satellites. The Centriolar Satellite (CS) organizer PCM1 binds the autophagy receptors GABARAP/GABARAPL2, through an LIR motif. This interaction drives the autophagy-mediated degradation of CS, preventing centrosome abnormalities and ensuring accurate mitosis. Upon doryphagy/autophagy impairment, CS accumulate and cause centrosome fragmentation, which results in aberrant mitosis and genomic instability. Mitotic-defects could also lower the tolerance threshold of these cells to mitosis-targeting drugs. The hypothesis that doryphagy may affect cell migration and ciliogenesis, in addition to mitosis, is intriguing.

Recent findings functionally link CS to the "cell´s sensory antenna" – the primary cilium. Early on, CS were observed to localize at the base of the cilium,[7] namely the basal body, which shares its core components with the centrosome. Despite this evidence, a role for CS in the formation of the cilium (ciliogenesis) was long suspected, rather than proven. Lately, loss-of-function experiments showed that intact CS are necessary for efficient ciliogenesis, most likely because they regulate the ciliary protein-content.[8] Although the mechanism underlying its selective degradation remains elusive, the CS component and cilium regulator OFD1 has been described as an autophagy substrate.[9] Interestingly, our data point at doryphagy as the mechanism responsible for OFD1 degradation, although the relevance to ciliogenesis has not been investigated yet.

In addition to its mitotic function, the centrosome is the compass of the cell. Accordingly, it affects cell migration and polarization. Note that loss-of-function models of CS also show defective neuronal migration and cell organization in 3D spheroid culture.[8,10] This lends strong support to CS interfacing with these centrosome-related processes – likely through its regulation of the centrosome – and leaves us wondering if doryphagy plays a role in these contexts as well. If that is the case, doryphagy may also affect the capability of cancer cells to metastasize. Given that the role of autophagy in cell migration and metastasization is context-dependent and, at times, controversial, it would be interesting to know where doryphagy stands in this regard.

Because CS are exclusive to vertebrates, researchers hypothesize that they were acquired as additional regulatory mechanisms to keep in check the centrosome/cilium, and thereby prevent the associated diseases.[8] In such a case, doryphagy may be implicated in those diseases too. Along the same lines, mutations in some CS proteins are associated with microcephaly (a neurodevelopmental disease),[11] suggesting that doryphagy could play a role in this context as well. Although these links are correlative, they urge further study on the possible relevance of doryphagy in these diseases.

In sum, we identified a new type of selective autophagy, namely doryphagy, responsible for CS turnover and homeostasis. Doryphagy prevents centrosome aberrations and inaccurate mitosis, thus avoiding genomic instability. While shedding new light on CS turnover and homeostasis, our study also suggests that coupling autophagy- and mitosis-targeting drugs may be a promising therapeutic strategy in cancer. Also, since CS interfaces with other cellular components (centrosome and cilium) and impacts several cellular processes (mitosis, ciliogenesis, migration and cell polarization), we foresee a plethora of physiological and pathological contexts in which doryphagy may be relevant.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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ORCID

Valentina Cianfanelli http://orcid.org/0000-0002-3857-9463
Francesco Cecconi http://orcid.org/0000-0002-5614-4359

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