

Scatter and Shatter: Centrosome Declustering is an Attractive Chemotherapeutic Strategy

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Editorial

The centrosome is a non-membranous organelle often found near the cell center, as per its namesake. It consists of two orthogonally-oriented centrioles enmeshed within a conglomeration of proteins called the pericentriolar material (PCM). Despite its diminutive size, the centrosome assumes a highly influential position in metazoan cells, serving as the major microtubule organizing center (MTOC). As such, the centrosome impacts a vast array of cellular processes, such as mitotic spindle formation and orientation, cell polarization, directional migration, cell signaling through the primary cilium, and locomotion via flagella [1]. Furthermore, the centrosome serves various MTOC-independent functions in cell cycle progression, such as G1/S transition, mitotic entry, anaphase onset, and cytokinesis. Consequently, disturbances in centrosome function typically engender far-reaching consequences.

Among the manifold derangements found in cancer cells, abnormalities of the centrosome constitute some of the most universal perturbations across malignancies. A great diversity of solid and hematological cancers feature structural and functional aberrancies of the PCM (e.g., altered composition, increased mass, enhanced microtubule nucleation capacity) and centrioles (defective barrel structure, misorientation, increased or decreased length or number) [2]. Moreover, centrosomes are oftentimes themselves excessively numerous (i.e., >1 pre- or >2 post-S phase), a condition termed centrosome amplification (CA).

An emerging notion envisions centrosomal abnormality, in particular CA, as primary drivers of tumorigenesis, including the acquisition of metastatic potential. CA is present in pre-malignant and pre-invasive lesions, suggesting it is an early event in tumorigenesis, and correlates with tumor aggressiveness [2]. Furthermore, CA may be capable of initiating tumor formation, as demonstrated in a fly model [3]. Recent studies have uncovered that CA drives chromosomal instability (CIN) by giving rise to a transient multipolar intermediate during mitosis, which predisposes the cell to merotelic MT-kinetochore attachments [4,5]. These erroneous attachments promote low-grade chromosome missegregation and aneuploidy (e.g., whole chromosome gain or loss), which may equip the cell with a malignant phenotype. In addition to promoting CIN, we suspect that CA benefits cancer cells via other, as yet incompletely elucidated mechanisms. For instance, induction of CA disrupts cell polarity in *Drosophila* neuroblasts [3], and loss of cell polarization may facilitate epithelial mesenchymal transition [6].

Despite this host of advantages, CA is not without liabilities for cancer cells—ones that can be exploited pharmacologically. The multipolar intermediate that forms during early mitosis when supernumerary centrosomes are present is usually short-lived, as many cancer cells are capable of clustering excess centrosomes at two poles to form a pseudo-bipolar spindle [7]. However, if clustering is suppressed the multipolar state persists, which may lead to death by prolonged mitotic arrest or multipolar mitosis [8]. It is likely that prolonged mitotic arrest may trigger apoptosis by accumulation of pro-apoptotic factors or those that promote the proteasomal degradation

of anti-apoptotic factors consigning the cell to its own demise. On the other hand, a multipolar division, especially one of high grade, may yield more than two daughter cells with aneuploidy too severe to be survived. To avoid the potentially fatal consequences of persistent multipolarity, cancer cells often cluster centrosomes at opposite poles to form a pseudo-bipolar spindle. These centrosome clustering mechanisms are either absent in or dispensable to non-transformed human cells that lack extra centrosomes. Strikingly, both pre-invasive lesions as well as mature tumors show the persistent presence of supernumerary centrosomes that must coalesce into two polar groups to successfully negotiate the crucial process of mitosis. Cancer cells' reliance on the inventive strategy of centrosome clustering for their survival thus constitutes a vulnerability that can be exploited for therapeutic intervention at both early and late stages of the disease. Importantly, inhibition of centrosome clustering in cancer cells should provide tumor-selective chemotherapy that nimbly decimates diseased cells only, and thus spares cancer patients of the devastating side-effects associated with traditional, non-selective remedies.

A logical next-step for drug development is to identify those clustering molecules in cancer cells that do not serve additional functions critical to healthy cells. One such protein is the microtubule cross-linker, HSET, whose inhibition produces persistent multipolarity and cell death in cancer cells with CA but not in normal or transformed cells lacking CA. Unfortunately, at present other known clustering factors (e.g., astral microtubules, actin, cell polarity proteins, focal adhesions, and microtubule-kinetochore attachment proteins) are vital to healthy cells and thus are not ideal chemotherapeutic targets. Clustering factors and mechanisms have been the subject of several recent reviews [9].

Another means of attack is to determine the mechanisms of action of known centrosome declustering drugs, which have demonstrated high chemotherapeutic efficacy along with low toxicity to healthy cells. This knowledge could pave the way for the rational design of similar agents or optimization of existing ones. Putative declustering drugs, including griseofulvin (a *Penicillium*-derived tubulin binding agent), noscapinoids (*Papaver*-derived microtubule-modulating agents), and PJ-34 (a phenanthrene-derived PARP inhibitor), scatter supernumerary centrosomes, perhaps by inhibiting centrosome clustering mechanisms. Alternatively, these agents may cause disruption of centrosome integrity, thereby inducing multipolarity without bonafide declustering

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of centrosomes. For instance, griseofulvin induces spindle multipolarity in cells that typically do not display CA (e.g., HeLa cells) [10], perhaps through centrosome shattering. Regardless of the mechanistic details, the hallmark of these agents is induction of spindle multipolarity and associated mitotic arrest perhaps followed by metaphase catastrophe or apoptotic cell death.

In summary, we believe that declustering drugs represent a wellspring of chemotherapeutic potential, considering their cancer cell-specific nature. In particular, these agents should be most effective against tumors with a high incidence of centrosome amplification, such as bladder, blood, bone and soft tissue, breast, prostate, colon, pancreas, and testicular malignancies. Since CA is often an early event in tumorigenesis, declustering drugs may be useful even early in the carcinogenic process, perhaps turning out to be chemopreventive. Moreover, considering the importance of centrosomes in polarized cell migration (a necessary step in metastasis), these agents may even prove to be potent anti-metastatic drugs. Altogether, we are optimistic that these novel centrosome-targeted chemotherapeutics, whether used as single agents or in combination with more traditional ones, will yield better patient outcomes for cancer patients early and late in the disease process.

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