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On The Origin Of Centrosome Amplification And Chromosomal Instability In Cancer

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The development and progression of malignant tumors involves numerous changes in disparate normal cellular processes, including: the control of cell proliferation and senescence; hormone and/or growth factor dependence; cell-cell, cell-extracelluar matrix, and parenchymal/stromal cell interactions; motility characteristics; and DNA damage surveillance and repair mechanisms. Oncogene activation and loss of tumor suppressor function are important underlying causal factors in cell transformation, however, they fail to account for the variety and extent of cellular changes observed in aggressive malignant tumors, or to explain the emergence of tumor cell phenotypic heterogeneity and the development of resistance to therapeutic treatments. Attention to this complicated issue in tumor biology has recently refocused interest on the origin of large-scale alterations in chromosome number and 'combinations' (aneuploidy) that were first recognized to be characteristic of cancer cells over a century ago. Indeed it is humbling for a modern cell biologist to realize that Theodor Boveri, armed only with a light microscope and keen skills of observation, defined the forefront of inquiry in tumor biology. In his classic treatment on the origin of malignant tumors [1], Boveri first formulated the concepts of a *mitotic checkpoint*, loss of heterozygosity of *tumor suppressor genes*, and dominant acting *oncogenes*. Importantly, he also proposed that gross changes in the compliment of chromosomes (*aneuploidy*) could account for the development of the cancer cell phenotype thereby playing a causal role in the development of cancer (see excerpt, below).

> "….in every normal cell there is a *specific arrangement for inhibiting* which allows the process of division to begin only when the inhibition has been overcome by a special stimulus (*mitotic checkpoint*)….Cells of tumors with unlimited growth would arise if those 'inhibiting chromosomes'…or even perhaps of only an abnormal relative amount of their material… were eliminated (loss of heterozygousity in *tumor suppressor genes*)…(and to suggest) the existence of chromosomes which *promote* division (*oncogenes*)….(and finally that)….abnormal mitoses may bring about an immense number of different chromosome combinations (*aneuploidy*)…. as would make a cell into a tumor cell."

The orgin of these concepts are only a sampling of Boveri's remarkable prescience on the 'problem of cancer'. Boveri's knowledge of tumors was largely based on the published studies of his contemporaries. Nonetheless, based on his studies on abnormal early development in the sea urchin following dispermic fertilization, he proposed a mechanistic explanation for the origin of aneuploidy in cancer through *asymmetric mitoses* and/or *multipolar mitoses* due to "an abnormal increase of centrosomes." Despite Boveri's early prediction, the role of abnormal centrosome behavior in the origin of aneuploidy in cancer has only recently become an area of active investigation.

Centrosomes contain a pair of centrioles that normally duplicate once in each cell cycle to produce the two centrosomes that function as mitotic spindle poles during cell division. As cells complete the final stage of cell division, each daughter cell inherits one spindle pole, which functions as the

centrosome for that cell during the next cell cycle. Therefore, a strict coupling of the centrosome, DNA, and mitotic cycles is essential not only for equal segregation of sister chromatids, but also for the equal segregation of centrosomes.

Recent studies reveal that centrosome defects, including an excess number of centrioles, increased microtubule nucleation capacity, and inappropriate phosphorylation of centrosomal proteins, a condition termed '*centrosome amplification*,' are indeed common features of malignant breast tumors, and solid tumors in general (reviewed in [2]). There are two current models for the origin of centrosome defects in the development of cancer. In the first, centrosome amplification arises through failure of cytokinesis and the consequent failure of equal partition of sister chromatids and spindle poles into daughter cells. In this model, a single 4N daughter cell inherits both spindle poles, instead of just one, to yield two functional centrosomes – this scenario mimics the dispermy experiments of Boveri [3,4]. The two centrosomes double again in the next cell cycle to yield four functional spindle poles and multipolar mitosis. Centrosome amplification arises in the second model through a deregulation of the centriole duplication cycle leading to centrosomes with supernumerary centrioles. In this model, disruption of key cell and/or centrosome cycle regulators may play a causative role. These models are not mutually exclusive and may operate independently or sequentially in the development of cancer. Centrosome amplification leads to an increased frequency of multipolar mitosis and consequent chromosomal instability, and therefore, is one mechanism by which aneuploidy and phenotypic variability arise in the development of cancer [5].

The tumor suppressor, p53, and cyclin/cdk cell cycle pathways regulate centrosome homeostasis by ensuring the integrity of the G1/S and G2/M cell cycle checkpoints. Loss of p53 function alone is not sufficient to cause the development of centrosome amplification, but rather failure of the G_1/S checkpoint activation following genotoxic stress is required to induce centriole over-duplication [6]. This mechanism may play an important role in the development of centrosome amplification during cancer development. However, these findings also have important clinical implications for the treatment of cancer because they suggest that tumor cells with defective G_1/S and/or G2/M cell cycle checkpoint functions may develop or exacerbate centrosome amplification following treatment with genotoxic anticancer drugs. This process may facilitate the development of higher clonal heterogeneity leading to chemoresistence and poor outcome. To overcome the complications associated with centrosome amplification for a subset of cancer patients, treatment with cdk inhibitors in combination with anticancer genotoxic drugs may provide an attractive therapeutic approach.

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