History of link between centrosome abnormalities and cancer

1914 Theodor Boveri proposed a direct link between centrosomal abnormalities and both the aneuploidy and loss of tissue architecture that are typical of human tumors.

- Numerical and/or structural centrosome abnormalities can cause mis-segregation
- Centrosome abnormalities are expected to affect cell shape, polarity, and motility. (tissue architecture)
Centrosome

Supernumerary Centrosomes in Cancer

Centrosome Duplication
A schematic comparison of a | the centrosome cycle and b | the chromosome cycle. Both the centrosome and the complete genome need to be duplicated once, and only once, in every cell cycle. Loss of coordination between the two cycles inevitably leads to chromosome missegregation or changes in ploidy.

Mechanisms of Centrosome Amplification
Centrosome Clustering

- In mitosis, supernumerary centrosomes can form multipolar spindles, which occur in many tumor types and have long been associated with CIN and tumorigenesis.
- Recent findings show that multipolar divisions and the resulting CIN undermine cell viability, frequently leading to cell death.
- To avoid cell death many cancer cells induce supernumerary centrosome clustering into two spindle poles, enabling bipolar cell division.

Mechanisms of Centrosome Clustering

Flies overexpressing SAK (a kinase important in centriole replication) had extra centrosomes in ~ 60% of their somatic cells. Larval brain cells from these flies generated metastatic tumors when transplanted into the abdomen of wildtype hosts.
In tissues where self-renewing asymmetric divisions are frequent, centrosome related disturbed stem cell division rather than induction of CIN might initiate malignant transformation.
Targeting centrosomal clustering as a novel anti-cancer therapy

• Supernumerary centrosomes occur frequently in a variety of neoplastic disorders but rarely in non-transformed cells

• Inhibition of centrosomal clustering with consequential induction of multipolar spindles and subsequent cell death could specifically target tumor cells
Kinetochore tension as a crucial centrosome clustering mechanism.

- Centrosome Cortical cues
- Direction of net dyenin force
- Direction of net kinetochore force
- Dynein
- Kinetochores (as central mass)

References


