

## **Kinase-independent role of cyclin D1 in chromosomal instability and mammary tumorigenesis**

Casimiro M., Di Sante G., Crosariol M., Loro E., Dampier W., Ertel A., Yu Z., Saria E., Papanikolaou A., Li Z., Wang C., Addya S., Lisanti M., Fortina P., Cardiff R., Tozeren A., Knudsen E., Arnold A., Pestell R.

*Kazan Federal University, 420008, Kremlevskaya 18, Kazan, Russia*

---

### **Abstract**

Cyclin D1 is an important molecular driver of human breast cancer but better understanding of its oncogenic mechanisms is needed, especially to enhance efforts in targeted therapeutics. Currently, pharmaceutical initiatives to inhibit cyclin D1 are focused on the catalytic component since the transforming capacity is thought to reside in the cyclin D1/CDK activity. We initiated the following study to directly test the oncogenic potential of catalytically inactive cyclin D1 in an in vivo mouse model that is relevant to breast cancer. Herein, transduction of cyclin D1<sup>-/-</sup> mouse embryonic fibroblasts (MEFs) with the kinase dead KE mutant of cyclin D1 led to aneuploidy, abnormalities in mitotic spindle formation, autosome amplification, and chromosomal instability (CIN) by gene expression profiling. Acute transgenic expression of either cyclin D1<sup>WT</sup> or cyclin D1<sup>KE</sup> in the mammary gland was sufficient to induce a high CIN score within 7 days. Sustained expression of cyclin D1<sup>KE</sup> induced mammary adenocarcinoma with similar kinetics to that of the wild-type cyclin D1. ChIP-Seq studies demonstrated recruitment of cyclin D1<sup>WT</sup> and cyclin D1<sup>KE</sup> to the genes governing CIN. We conclude that the CDK-activating function of cyclin D1 is not necessary to induce either chromosomal instability or mammary tumorigenesis.

---

### **Keywords**

Breast cancer, Chromosomal instability, Cyclin D1