Chromosomal instability (CIN), a hallmark of most human solid tumors, causes ongoing chromosomal gains or losses, leading to aneuploidy. Aneuploidy contributes to cancer progression, poor prognosis, and drug resistance. Targeting aneuploidy for cancer treatment requires understanding signaling pathways enabling aneuploid cell survival. Using *Drosophila* as a model, I investigated transcriptional responses to CIN and identified altered one-carbon metabolism, particularly S-Adenosyl methionine (SAM) pathways. Depleting *SAM* synthase in CIN cells induced apoptosis, reversible by spermine supplementation. Loss of polyamines heightened reactive oxygen species susceptibility and reduced autophagy, driving CIN cell death, suggesting polyamine inhibition as a therapeutic strategy. Additionally, I modeled neuronal aneuploidy in Drosophila, linking *Mad2* depletion in GABAergic neurons to increased aneuploidy, cell death, and seizure phenotypes, mitigated by antioxidants. Finally, we developed *Drosophila* lines expressing human *KCNT1* epilepsy mutations, demonstrating seizure phenotypes modifiable by cannabidiol. This establishes Drosophila as a model to study CIN-related diseases and *KCNT1* epilepsy.