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THE CITRATE LYASE PLAYS CONSERVED ROLES IN THE MAINTENANCE OF GENOME STABILITY

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We have previously shown that *scheggia (sea),* which encodes the fly ortholog of mammal mitochondrial citrate carrier SLC25A1, is required for preventing chromosome breaks in *Drosophila* and humans. To further investigate the conserved cross-talk between citrate metabolism and maintenance of genome stability, we have started to genetically dissect the pathway that yields cytosolic Acetyl-CoA formation from citrate. We thus focused on the ATP citrate lyase (ACL) enzyme that converts the citrate exported from mitochondria, in acetylCoA and ossalacetate. We found that in homozygous and hemizygous ACL mutant combinations histone acetylation was reduced. Moreover, mutant larval brains exhibited a significant proportion of hyperploid and tetraploid cells as well as chromatid and isochromatid breaks. In addition, a small portion of mutant anaphases were abnormal with respect to wild-type in that they displayed chromatin bridges and lagging chromosomes which are likely acentric. However, in contrast with extensive chromosome breakage elicited by *sea* mutants, depletion of DmACL gave rise to rare, spontaneous chromosome breaks (3% *DmACL,* N= 180), suggesting that loss of either Sea or ACL affects genome stability in different ways. Interestingly, feeding *DmACL* mutant larvae with 0.5 M citrate partially abolished chromosome defects indicating that, as observed previoulsy for *sea* mutants, intracellular levels of citrate can regulate chromosome dynamics in mitosis. To check if the mitotic defects influenced mitosis progression, both frequency of anaphases (AF) and mitotic index (MI) have been determinated. We have observed that *DmACL* mutants do not display any changes in either AF or MI mitotic parameter suggesting that chromosome segregation defects and breaks do not activate either SAC or DDR, respectively. Altogether, these observations indicated that DmACL function is required for a proper completion of mitosis in *Drosophila* mitotic cells.

Owing the high degree of conservation between DmACL and human ACL, we sought to determine whether ACL depletion affected chromosome behavior also in human primary fibroblasts. Very interestingly, human fibroblasts transfected with siRNA duplexes against ACL exhibited a significant number of hyperploid/tetraploid cells (30%; N= 100). As this phenotype is very similar to that elicited by *DmACL* mutant cells, we can conclude that DmACL/ACL, plays an evolutionary conserved role in controlling chromosome stability.