Supplemental Figure 1

A model for conjugation of topoisomerase IIα with SUMO-2/-3 proteins within mitotic chromosomes. Activity of topo 2α at the axes is required for full removal of the last catenanes connecting chromatids before onset of anaphase. Also, genetic and biochemical evidence implicate conjugation of topo 2 to SUMO proteins in chromatid cohesion and separation during M stage (cf references in the text). Topo 2α dimers that localize at the chromosome cores/axes and centromeric regions are transiently conjugated with SUMO-2/-3 proteins exclusively during their involvement in DNA strand-passage/religation activities. Thus, the fraction of topo 2α that is modified by SUMO-2/-3 is almost undetectable under steady-state conditions (no drug; *left panel*). However, stabilization of catalytic intermediates with specific topo 2 inhibitors (etoposide, doxorubicin, ICRF-187) allows accumulation of topo 2α-SUMO-2/-3 conjugates (cleavage complexes, closed clamps; *right panel*). Conversely, abrogation of initiation of catalysis (aclarubicin, merbarone) by preventing subsequent formation/stabilization of catalytic intermediates in response to inhibitors acting downstream (etoposide, doxorubicin, ICRF-187) precludes accumulation of SUMO-2/-3 proteins at mitotic chromatin. We propose that during mitosis topo 2-specific drugs act, at least partially, by altering the dynamics of a subpopulation of topo 2α that becomes conjugated with SUMO-2/-3 in a PIASy-dependent fashion at the chromosomal axis; this subpopulation should be critically involved in chromatid separation. This model highlights the mitotic chromosomal axis both as a domain involved in SUMO-modification and as a target for topo 2-specific drugs.