DNA double strand breaks (DSBs) are produced by normal physiological cellular processes and are induced by genotoxic agents, among which several chemotherapeutic drugs. Misprocessing of DSBs leads to pathological alterations and to the elevated genome instability observed in cancer cells. DSBs are mainly repaired by homologous recombination (HR) and by non homologous end joining (NHEJ). The proper balance between the two pathways is modulated by 53BP1 recruitment through an elusive mechanism mainly based on chromatin status around the break. Here we report that DAXX, a chaperone involved in loading H3.3 mainly at telomeric and centromeric regions, plays a fundamental role at DSBs. H3.3 is a histone variant that differs from the classical H3.1 by five amino acids but several post translational modifications. Both DAXX and H3.3 are mutated in glioblastoma, the most common and aggressive form of cancer in the central nervous system. We found that in human cells, DSBs-induced ATM/ATR-dependent phosphorylation of DAXX at specific residues promotes DAXX binding to and deposition of H3.3 on chromatin nearby DNA breaks. Enrichment of H3.3 at damage sites regulates 53BP1 relocation at DSBs and the choice between HR and NHEJ repair pathways. H3.3-specific post translational modifications, particularly K36 methylation, play a key role in these events. Importantly, several H3.3 mutations that characterize human glioblastomas are known to hit K36 post translational modification. Altogether these findings reveal that DAXX and H3.3 are critical in determining DSB repair pathway choice, and their mutation may promote tumorigenesis enhancing genome instability. Now, the purpose of our studies is the analysis of DNA repair efficiency and fidelity in human cells expressing DAXX and H3.3 mutations associated with cancer. These results could be relevant for diagnosis and therapy of some particularly aggressive forms of cancer.

References: Daxx histone chaperone modulates double strand breaks repair pathway choice through H3.3 deposition. Aliprandi S., Zannini L., Delia D., Muzi Falconi M, Buscemi G. Submitted

Keywords: DNA repair, Double strand breaks, Histone variant

Contacts: Giacomo Buscemi, E-mail: giacomo.buscemi@igm.cnr.it, Phone: 0382546327; Laura Zannini, E-mail: laura.zannini@igm.cnr.it, Phone: 0382546363.