Neuron-specific methylome analysis reveals epigenetic regulation and tau-related dysfunction of BRCA1 in Alzheimer’s disease.

Schematic illustration summarizing our current hypothesis regarding Aβ-induced DNA damage, tau, and epigenetic regulation of BRCA1 in AD. In normal brain without Aβ or tau accumulation, there is no need for BRCA1 up-regulation (Left). At an early stage of AD with no accumulated tau, BRCA1 efficiently repairs DNA DSBs induced by toxic Aβ (Middle). However, at an advanced stage of AD, cytoplasmic aggregated tau sequestrates BRCA1 to an insoluble fraction, resulting in its dysfunction (Right). While neurons try to cope with this situation by up-regulating expression of the BRCA1 gene through epigenetic mechanisms, they are eventually overwhelmed by the accumulation of DNA damage.