Due to external and internal exposures, cells accumulate enormous amounts of damage to DNA every day. This damage can be the cause of aging, neurodegeneration and cancer, or cell death, if it persists in the genome. DNA damage triggers a large cascade of events that include a variety of processes and signaling pathways including DNA repair. Cells have intricate and efficient processes for DNA repair to prevent these outcomes, but it is a matter of time. The damage accumulates both in the nuclear and mitochondrial DNA, and mitochondrial function is affected by both types. Lately, evidence supports that there is a signaling cascade from the nuclear DNA damage to mitochondrial function, and thus directly to the bioenergetic regulation of cells. This is seen across species from human to worms. We find that some DNA repair defective diseases with severe neurodegeneration have mitochondrial defects. Our studies involve cell lines, the worm (c.elegans), and mouse models and include the conditions Xeroderma pigmentosum group A, Cockaynes syndrome, Ataxia telangiectasia and others. We find a pattern of hyper parylation, deficiency in the NAD+and Sirtuin signaling, and mitochondrial stress. This involves a defect in the ability remove damaged mitochondria, a process called mitophagy, which is a sub pathway of autophagy. We are pursuing mechanistic studies of this signaling and also find that interventions at different steps can improve mitochondrial health and neurodegeneration. The mechanisms involved and some promising interventions inclu