Mammalian mitochondrial genome (mtDNA) is critical to basic cellular functions as it encodes the key subunits of the oxidative phosphorylation system (OXPHOS). DNA in mitochondria (mtDNA), just like in the nucleus must be faithfully replicated and mistakes, i.e. mutations, in mtDNA result in devastating mitochondrial diseases. 1 in about 2000 individuals is at risk of developing a mitochondrial disease sometime in their lifetime, making it one of the most common groups of metabolic disorders. Yet, to date, there is no cure or approved treatment for mitochondrial diseases. Stability of mitochondrial genome depends on the accuracy of mtDNA replication which is caried out by the dedicated set of enzymes forming multi-component molecular machine called replisome. These proteins come together to form mitochondrial DNA replication complex. Although the essential components of mitochondrial replisome are known, the structure and elaborate temporal and spatial orchestration of assembly and disassembly within this fundamental macromolecular machine is not understood. The long-term goal of this project is to understand the structural architecture of human mitochondrial replisome, functional cooperation between replisome components and mechanistic basis for origins of human disorders arising from mitochondrial dysfunction.