RESEARCH ACTIVITY (G. LIBERI)

DNA replication forks encounter several transcription-dependent obstacles that must be bypassed to complete genome duplication before cell division. Failure to overcome such transcription barriers leads to fork arrest and collapse, a pathological condition known as replication stress, which is a hallmark of cancer and other human diseases.

We are interested in understanding the mechanisms that coordinate replication with transcription and thus prevent transcription-induced replication stress. We have shown that one of these mechanisms relies on the activity of the evolutionarily conserved DNA/RNA helicase Sen1 of budding yeast, called Senataxin in human. Senataxin is a potential tumor suppressor gene and is mutated in certain neurological disorders, including a type of Ataxia (AOA2) and a type of Amyotrophic Lateral Sclerosis (ALS4). We have shown that Sen1 associates with replication forks and, by counteracting the formation of recombinogenic RNA:DNA hybrids, preserves the integrity of forks encountering head-on RNA polymerase II-transcribed genes. We have recently shown that transcription has a profound impact on DNA replicon dynamic in *sen1* mutants: both divergent sister forks within a replicon are arrested, while one of the two fork clashes with a highly expressed gene as the consequence of the coupling between sister replisomes activities. Forks arrested by transcription are rescued by the local activation of dormant origins of replication and specific fork protection complexes that counteract nuclease-mediated fork resection.

We are using genetic and genomic approaches combined with analysis of the replication intermediates by 2D gel technique and Electron Microscopy to further explore the mechanisms and factors that preserve the integrity of fork colliding with transcription and the pathological transitions occurring at forks arrested by transcription in *sen1* mutants.