

CCS Highlights 2022

The overarching goal of the Center for Chromosome Stability (CCS) is to define the mechanisms by which eukaryotic cells maintain the integrity of their genome. This fundamental research aim is complemented by a more translational goal of understanding how chromosome instability not only promotes the emergence of human disease, but also might be exploited to develop new therapeutic interventions. In this regard, the center has interests in a variety of pathological conditions, including neurodegenerative diseases, fertility disorders and cancer. Many of our studies focus on how cells respond to intrinsic or extrinsic forms of stress that target genomic DNA, such as occurs as a result oncogene activation during neoplastic transformation of cells. In addition, we investigate how stress-induced DNA damage leads to changes in chromosome number and structure, which are known drivers of human disease. As part of these goals, we have a longstanding interest in understanding how problematic loci in the human genome (the so-called 'enemies within') create genomic rearrangements due to their intrinsic instability. This begs the question of why these 'enemies within' are so highly conserved in evolution, despite appearing to pose a continued threat to genome integrity.

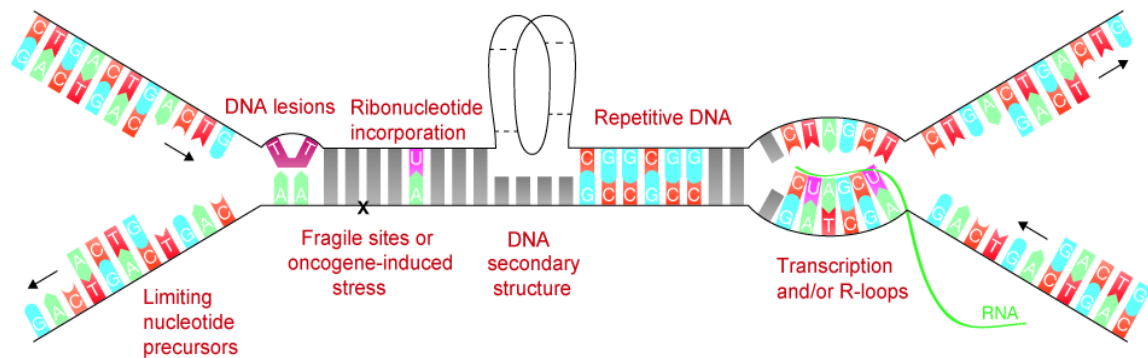


Figure 1: Depiction of one of the major topics under study in the CCS: the cellular response to perturbation of genome duplication (DNA replication). This process is frequently perturbed when the replication machinery encounters DNA lesions or DNA secondary structures, or when replication comes into conflict with the transcription machinery simultaneously using the same DNA template. One major area of interest is to understand how difficult-to-replicate regions of the human genome, such as fragile sites, trigger genome instability and disease.

In 2022, the CCS bounced back from the disruptive effects of the pandemic and has had a very positive year in terms of achievements. Our new group leader, Tom Miller, is now well embedded in the center and in our host department (ICMM). Most gratifyingly, Tom succeeded in obtaining a major starting grant (Hallas Møller Emerging Investigator from the NNF) to establish and develop his group over the next 5 years. Other notable grant awards were made to Eva Hoffmann, Mads Lerdrup and Ying Liu, while two CCS postdocs obtained prestigious EMBO Long Term Fellowships. The CCS has also produced several high impact publications in 2022, including a paper in *Nature* from the Hickson and Liu groups, which was the culmination of several years' work to develop the methodology to manipulate individual human chromosomes *in vitro* using novel biophysical methods. The Toledo group also produced a major publication in *Molecular Cell* that we believe will have a profound influence on the field as it challenged existing thinking about how cells recognize whether the process of DNA replication has been completed or not before embarking on cell division.