The Genomic Instability Laboratory is interested in understanding the molecular mechanisms causing cancer and other age-related diseases, in order to provide the knowledge needed to develop novel treatments for these diseases. Initially, we focused on the study of replicative stress, a type of DNA damage that fuels genomic instability and is present in many types of cancer. Those studies led to important contributions to basic research and also led to the development of potent and selective ATR inhibitors that were transferred to the pharmaceutical industry for clinical development. Subsequent to elucidating the mechanisms of resistance to ATR inhibition by genetic screens, our Group gradually developed an interest in understanding how cancer cells develop resistance to therapies, and how we can target therapy-resistant cancer cells. In addition, we are actively involved in exploring the contribution of nucleolar stress to cancer and neurodegeneration.

“In 2023, we discovered new biomarkers that predict sensitivity to SETD8 inhibitors and significantly advanced in our understanding of nucleolar stress as a driver of ageing and neurodegeneration.”
RESEARCH HIGHLIGHTS

Targeting SETD8 in tumours with high rates of ribosome biogenesis

A large number of the driver mutations found in tumour cells occur in genes related to chromatin regulation, a fact particularly relevant for paediatric tumours, which frequently harbour mutations linked to cell fate and differentiation. These findings have revitalised the efforts to develop drugs targeting epigenetic regulators ("epidrugs") and today, epigenetics is a very active area in the development of cancer therapies. In this regard, SETD8 is a histone methyltransferase known to play important roles in DNA replication and repair, and is overexpressed in a wide range of cancers. Moreover, SETD8 has been identified as a specific vulnerability of several tumours of bad prognosis, such as neuroblastoma or MYC-driven medulloblastoma. This research triggered additional efforts to develop SETD8 inhibitors, and several compounds have already been generated. However, the available molecules present poor pharmacological properties and none have progressed to clinical development. In our Group, we have discovered novel SETD8 inhibitors (SETD8i) and performed the first steps to characterise them. In 2023, we completed several CRISPR screens using both chemical and genetic approaches. These compounds are toxic, particularly efficacious for the killing of cancer cells with high levels of nucleolar activity. Conversely, their toxicity is alleviated in several CRISPR screens using both chemical and genetic strategies to target SETD8. These efforts revealed that the toxicity of SETD8 inhibitors is highest in cells with increased levels of nucleolar activity. Accordingly, these compounds are particularly efficacious for the killing of cancer cells with high MYC or mTOR activity. Conversely, their toxicity is alleviated upon MYC depletion or rapamycin treatment (FIGURE 1).

Nucleolar stress as a driver of ageing

Ribosome biogenesis is the most energy-demanding activity in a cell and takes place in the nucleolus. Accordingly, abnormalities in nucleolar activity or structure, collectively known as nucleolar stress (NS), have often been found in patients with several human diseases such as cancer or neurodegeneration. Although P53 contributes to NS toxicity, this stress ultimately kills cells by P53-independent mechanisms that remain to be deciphered. To investigate how NS triggers cellular toxicity, our Group used (PR) arginine-rich peptides, found in patients with amyotrophic lateral sclerosis (ALS) and other neurodegenerative pathologies, as inducers of this perturbation. We previously showed that PR-peptides accumulate at nucleoli and impair rRNA processing. These observations led us to hypothesise that reduced amounts of mature rRNA molecules could trigger an accumulation of free r-proteins. Indeed, proteomic analyses of the ribosome free-fraction of cells expressing (PR)97 peptides allowed us to confirm a significant increase in the levels of free r-proteins. Conversely, (PR)97-resistant cells have lower rates of ribosome biogenesis. Furthermore, targeting r-protein synthesis by mTOR inhibition or MYC depletion, the 2 main known regulators of ribosome biogenesis, alleviates (PR) toxicity in several cell lines. In mice, systemic expression of (PR)97 drives widespread NS and accelerated ageing (FIGURE 2), which is alleviated with rapamycin. Importantly, we discovered that the generalised accumulation of free r-proteins is a common outcome of NS, independent of its source. Overall, our work reports a unifying model to explain how NS kills cells independently of P53 and provides the first in vivo evidence to illustrate that NS accelerates ageing in mammals.

− PUBLICATIONS

FIGURE 1 The toxicity of SETD8 inhibitors correlates with nucleolar activity. (A) Results of a CRISPR screen in U2OS cells exposed to SETD8 inhibitors. (B) GO terms reflect that aspects related to nucleolar activity and ribosome biogenesis are enriched among the factors that modulate the sensitivity to SETD8 inhibition. (C) Depletion of MYC by siRNA in U2OS cells increases the resistance to SETD8 inhibition.