TELOMERE UNCAPPING AS A POTENTIAL NEW THERAPEUTIC TARGET FOR LUNG CANCER

Since unlimited cell division in cancer requires activation of mechanisms that ensure maintenance of telomere length, telomeres are considered anti-cancer targets. The targeting of telomeres in human cancer has been approached via targeting telomerase activity. However, therapeutic strategies based on telomerase inhibition to treat cancer will be effective only when telomeres shorten below a minimum length. We investigated whether the induction of telomere dysfunction, independently of telomere length, by targeting the TRF1 shelterin component could be used as a more universal way to block the growth of dividing cells. We found that the genetic ablation of Trf1 impairs the growth of p53-null K-RasG12V-induced lung carcinomas and increases mouse survival (FIGURE1). This is accompanied by induction of telomeric DNA damage, apoptosis, decreased proliferation, and G2 arrest. This tumour-suppressive effect of Trf1 deficiency occurs already at the first mouse generation and is independent of telomere length. We also showed that chemical inhibition of TRF1 could be achieved in vivo by using small molecules, which effectively impair the growth of already established lung adenocarcinomas without affecting mouse and tissue viability. Our results constitute proof of concept that acute telomere uncapping by means of TRF1 abrogation is an effective therapeutic strategy to block the growth of aggressive lung cancer.
Pulmonary fibrosis driven by telomere dysfunction

Idiopathic pulmonary fibrosis (IPF) is a degenerative disease of the lungs with an average survival, post-diagnosis, of 2-3 years. Mutations in components of telomerase or in proteins of the shelterin complex are found in both familial and sporadic IPF cases.

The lack of mouse models that faithfully recapitulate the human disease, however, has hampered new advances. We generated 2 independent mouse models that develop IPF owing to either Trf1 or p53 deficiency and identified telomeres as promising targets for new treatments.

A mutation in the shelterin component POT1 is responsible for cardiac angiosarcoma

Cardiac angiosarcoma (CAS) is a rare malignant tumour whose genetic basis is unknown. In collaboration with the CNIO Human Genetics Group and the Familial Cancer Clinical Unit, we have shown via whole–exome sequencing of a TP53-negative Li-Fraumeni-like (LFL) family including CAS cases, that a missense variant in the gene coding for the shelterin component POT1 is responsible for CAS. The same gene alteration is found in 2 TP53-negative Li-Fraumeni-like (LFL) families.

In TP53-negative LFL families, POT1 levels, abnormally long telomeres and increased telomere fragility, highlighting a new role of POT1 as a high susceptibility gene for prognosis and treatment in families with CAS.

Exacerbated collagen deposition and fibrosis as visualised by blue Masson-trichrome staining in the lungs of mice with severe telomere dysfunction (FIGURE 2). In the case of short telomeres, telomere-induced DNA damage, is sufficient for the development of full blown pulmonary fibrosis (FIGURE 2). We have provided proof of principle of the causal role of DNA damage stemming from dysfunctional telomeres in IPF development and identified telomeres as promising targets for new treatments.

PULICATIONS

- Kroon G, Masson-trichrome staining in the lungs of mice with severe telomere dysfunction was performed. The lung sections were stained with Masson-trichrome and visualised under a light microscope. Masson-trichrome staining is a commonly used method to stain connective tissue such as collagen. This staining can help in the diagnosis of conditions such as fibrosis, which is a common feature in pulmonary fibrosis. The Masson-trichrome staining in the lungs of mice with severe telomere dysfunction showed increased collagen deposition, indicating fibrosis.


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