The Challenge: How does the human genome work and why sometimes it does not?

Beyond the double helix

1. The human genome is a highly flexible molecule that can adopt different conformations.
2. In cancer, aberrant structures occur that drive oncogenic programs.
3. Alternative DNA structures named G-quadruplexes (G4s) can form in cancer cells and control gene expression.

The Strategy: Genome editing of cancer gene structures

Human kidney cells

- Normal
  - Structure retention
  - Gene expression
  - Protein recruitment
- Edited
  - Structure modification
  - Gene expression
  - Protein recruitment
- Substituted
  - Structure substitution
  - Gene expression
  - Protein recruitment

Profiling with next generation sequencing, we investigate through a series of genetic edits, the influence of G4s as regulatory elements of one of the most critical cancer genes (MYC), which controls how cancer cells divide.

The Results: New mechanism for cancer regulation

We provide robust evidence that G4 structures in the human genome are critical features required for cancer gene expression and are key molecular orchestrators operating as molecular master keys.

- A folded G4 is crucial to drive cancer gene expression.
- DNA structure is recognised by proteins in cells. Altering DNA conformation impairs protein recognition, resulting in defective cancer progression.
- Secondary structure dictates gene expression in a sequence unrelated manner.

Investigating DNA secondary structure is important for understanding cancer gene expression.

These results demonstrate that DNA structure constitutes a key layer of information, which changes our current understanding on gene regulation.

The Impact: Precision genome editing and early-detection

Understanding the detailed molecular mechanisms of DNA structure and gene regulation opens a new therapeutic window for cancer treatments and takes us closer to a future of early detection and precision genome editing tools.

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