A method for precisely tuning gene expression levels in mammalian cells

Researchers at the University of Oxford have developed a method for modulating gene expression in response to effector microRNAs.

Manipulating gene expression

The fascinating cellular diversification characteristic of metazoans relies on a milieu of sophisticated regulatory systems, which act to control gene expression with minute spatial-temporal precision. Errors in these programs can have serious developmental consequences and lead to the onset of numerous human diseases.

Currently, studies aiming to understand the role of gene-products in various biological processes or to engineer cells for therapeutic purposes have relied on gene knock-ins (KI), knock-outs (KO) and RNA interference (RNAi). However, they are not suitable for studying or engineering quantitative changes in expression levels. Therefore, there is a need to develop methods for precisely tuning gene expression in mammalian cells.

Cancer immunotherapy

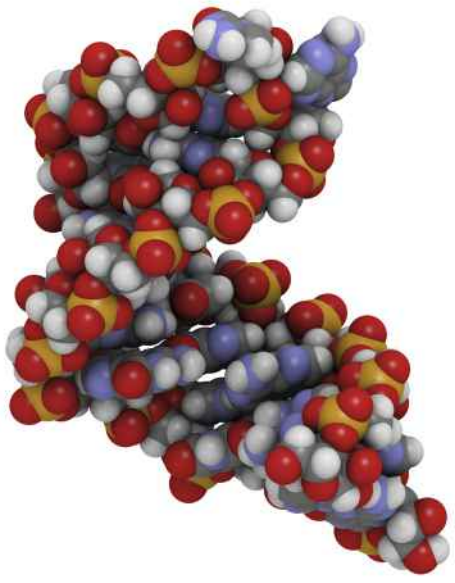
The co-inhibitory receptor *programmed cell death 1* (PD-1) plays a central role in the ability of tumours to cause T-cell exhaustion and escape immune surveillance. Checkpoint blockade therapies that suppress PD-1 signalling can improve the anti-tumour response but also unleash severe autoimmune reactions. PD-1 KO has equally detrimental effects and can, paradoxically, lead to increased exhaustion and impaired survival of T-cells via the compensatory up-regulation of other co-inhibitory receptors. Therefore, precise, stepwise and context-dependent regulation of co-inhibitory receptors expression could help realise the promise of T-cell engineering for next-generation cancer immunotherapies.

A new paradigm to precisely modulate gene expression

Researchers at Oxford have developed a new platform to precisely modulate gene expression that is applicable to a wide range of therapeutic applications. This approach relies on the engineering of synthetic microRNA response elements (MREs), which can harness the repressive potential of endogenous microRNAs to control the levels of user-defined target genes. By introducing defined mismatches in these synthetic MREs the team was able to tune the strength of endogenous miRNA-mediated repression and consequently gene expression output to within 0.02% of any desired level. This strategy could provide an ideal solution for preventing tumor-induced exhaustion of engineered T-cells while mitigating the risk of autoimmune reactions.

Benefits of this method:

- Intergration into existing manufacturing protocols for engineered T-cells;
- Precise tuning of gene expression;
- No exogenous interaction once the system is integrated into native genes or therapeutic transgenes;
- Reduced probability of off-target effects.



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