Scripps Research

Decoding cellular communications

to find new therapies for human diseases

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ABOUT THE LECTURE

A molecular and structural specialist, Scripps Research professor Xiang-Lei Yang underscored the importance of tRNA synthetases, a group of decoding machines that have evolved greater communication and coordination functions in the development of complex organisms. Yang demonstrated how irregularities in these machines may be at the root of several serious diseases, and how advances in gene therapy could provide precision medicines that reverse disease and restore healthy function.

TOP TAKEAWAY POINTS

1. **Every cell's central biological principle is to translate the language of our DNA code into the language of our proteins,** the building blocks that carry out all our day-to-day functions. tRNA synthetases are the main characters controlling the translation of these languages.

2. **tRNA synthetases are critical because they connect the nature of our DNA and proteins with the nurture of our external environment.** In the face of external challenges (e.g., nutrient depletion or low oxygen), tRNA synthetases respond by adjusting which proteins get produced and how they are used.

3. **Under low oxygen conditions, the growth of new blood vessels occurs, which is a hallmark of cancer.** Mutations identified in certain tRNA synthetases prevent them from inhibiting this process, potentially leading to runaway tumor growth. Preliminary work in animal models shows adding a modified type of tRNA synthetase can restore this function and reduce tumor burden.

4. **Different mutations in tRNA synthetases are responsible for Charcot-Marie-Tooth disease (CMT), a debilitating neurological condition.** These mutations affect how the tRNA synthetases machinery interacts with other proteins, causing impaired nerve function and heightened response to stress factors. Promising rodent studies suggest that CMT disease can be impacted by introducing a modified form of tRNA synthetase that dampens the heightened response.

5. **In the lungs, tRNA synthetases have anti-inflammatory actions that help repair tissue.** An autoimmune disease (antisynthetase syndrome) that targets these tRNA synthetases causes the loss of this anti-inflammatory role, leading to interstitial lung disease. A fusion protein delivering tRNA synthetase has yielded positive results in pulmonary sarcoidosis, reducing lung stiffness and boosting respiratory function. The development of this landmark molecular therapy would represent the very first tRNA synthetase-based medicine.

THE FRONT ROW
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