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News Release & Factsheet

SMART's discovery opens gateway to developing drugs against Tuberculosis

- Discovery of a new fundamental mechanism that controls when and how bacteria go into dormancy
- Impact includes the development of drugs that can target this pathway; drugs that could serve as antibiotics or reverse drug resistance in any bacteria (beyond TB) that goes into dormancy

1. Singapore – Scientists at the Singapore-MIT Alliance for Research and Technology (SMART) [新加坡-麻省理工学院科研中心] have made a fundamental discovery of a mechanism that helps cells to rapidly divert resources in emergency situations, rendering the bacteria dormant. Many bacteria, including strains that cause TB, use this mechanism to enter a latent-like state (non-replicating persistence) which allows them to survive in hostile environments when deprived of oxygen or nutrients. This dormant state renders antibiotics ineffective as current drugs work on the premise of killing bacteria that are active and growing.

2. This discovery in systems biology, led by 32-year-old Singaporean researcher, Dr Chionh Yok Hian [蒋育贤] translates to possibilities that could:

    a. Target this pathway with new drugs/antibiotics;
    b. Reverse drug resistance;
    c. Prevent TB infection (as an example) from going into its latent state so as to prevent it from flaring up in old age (estimated 29% of Singaporeans have Latent TB Infection);

3. Dr Chionh, SMART Postdoctoral Associate, was the lead author of the paper "tRNA-mediated codon-biased translation in mycobacterial hypoxic persistence" which was published in the prestigious *Nature Communications* in Nov 2016. His research started in 2010.

How the mechanism works

4. Directed by Prof Peter Dedon, SMART Principal Investigator (PI) of Infectious Diseases (ID) Interdisciplinary Research Group (IRG) and current Resident PI, the SMART scientists studied a type of bacteria known as *Mycobacterium bovis* (which is actually the weaker strain of TB used in the BCG vaccination).

5. Cells respond to different types of stress with different mechanisms. In this study, the SMART scientists found that certain tRNA modifications went up dramatically when the bacteria were deprived of oxygen and stopped growing.

6. Dr Chionh says: "There are many mechanisms that cells use to make decisions. For instance, if my army sergeant commands me to jump, I need to make a decision to understand when to jump and how high to go. Similarly, there are many actions and reactions that take place when the cells are stressed. What I've done is analysed all the moving parts of TB-causing bacteria to understand how it survives the host immunity. Seeing how it all comes together allows me to determine the manner in which survival mechanisms are scheduled at the most fundamental level."

7. Prof Peter Dedon adds: “The basic genetic code determines what a cell makes. We discovered an alternative genetic code, very likely present in all bacteria, which assigns priority to the genes that are expressed. This enables the precise scheduling of gene products required to respond to starvation or to develop drug resistance.” See factsheet for scientific details of actual mechanism.

8. Since 2015, SMART has been collaborating with A*STAR’s Experimental Therapeutics Centre (ETC) to develop new classes of antibiotics that leverages this finding, in the hope of increasing our treatment options against drug resistant bacteria. This collaboration is partly funded by the SMART Innovation Grant.

9. This research was funded by the National Research Foundation Singapore under its Campus for Research Excellence and Technological Enterprise (CREATE) programme.

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About Singapore-MIT Alliance for Research and Technology (SMART)
[新加坡-麻省理工学院科研中心]
Singapore-MIT Alliance for Research and Technology (SMART) is a major research enterprise established by the Massachusetts Institute of Technology (MIT) in partnership with the National Research Foundation of Singapore (NRF) since 2007. It is the first entity in the Campus for Research Excellence and Technological Enterprise (CREATE) developed by NRF.

SMART serves as an intellectual hub for research interactions between MIT and Singapore. Cutting-edge research projects in areas of interest to both Singapore and MIT are undertaken at SMART. SMART comprises an Innovation Centre and five Interdisciplinary Research Groups (IRGs): BioSystems and Micromechanics (BioSyM), Center for Environmental Sensing and Modeling (CENSAM), Infectious Diseases (ID), Future Urban Mobility (FM) and Low Energy Electronic Systems (LEES).

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Scientific Factsheet

Found in translation: Cells schedule protein synthesis using a hidden genetic code and dozens of RNA decorations

Cells in all living organisms are programmed to adapt to changes in their environment, such as altered temperature, nutrient availability and hormone stimulation. At the heart of these adaptive programs are the fundamental steps by which genes are expressed as the protein machinery that controls cell growth and behaviour – the "central dogma of biology": Genes are transcribed into messenger RNAs (mRNA) that are then read by the translation machinery to convert the three-letter genetic code into strings of amino acids that make up proteins. The key features in translating the genetic code into protein are the three-letter "codons" in mRNA. These are decoded by transfer RNA (tRNA) molecules that each read a different three-letter codon and carry the appropriate amino acid for that codon. This enables each specific an amino acid building block to be inserted into the growing protein in the correct order. The translation process takes place when ribosomes assemble on the mRNA and guide the tRNAs to read the genetic code, with each tRNA reading its codon in the series dictated by the mRNA and adding the next amino acid to the growing protein. SMART researchers have now discovered a new mechanism that cells use to schedule protein production.

Scientists have long assumed that the genetic code simply specified a protein for translation, with environmental signals telling the cell when to transcribe new mRNAs to produce new proteins to adapt to the new environment. A stochastic model. SMART researchers have now discovered a new mechanism that cells use to prioritize protein production in response to environmental changes – a two-part mechanism in which an alternative genetic code is read by specific tRNAs that are chemically reprogrammed to read the new genetic code. This mechanism allows the cell to adapt quickly to a changing environment by prioritizing the production of the proteins most important to the moment.

The first part of this mechanism – a "code of codons" – exploits the so-called degeneracy of the genetic code. One of the puzzling features of the genetic code is that there is usually more than one codon for each of the 20 amino acids, with up to six three-letter codons specifying a single amino acid and a total of 61 codons in all. These different codons are read by different tRNAs each carrying the same amino acid. Since the codons all specify the same amino acid, they all have the same meaning and are said to be synonymous. Various theories have been put forward to rationalize the existence of synonymous codons, such as the idea that the frequency of use of individual synonymous codons in an organism's genome reflects the abundance of the matching tRNAs.

The second part of the new translation scheduling mechanism involves another poorly understood feature of the translation machinery: the presence of dozens of different chemically-modified building blocks in the tRNA molecules. Like the DNA that contains the genome for each cell, all RNA molecules are linear strings comprised of four basic building blocks – the A, C, G and U ribonucleosides – the sequence of which is dictated by their corresponding genes in the genome. The tRNA molecules are about 70 ribonucleosides long, with three of the ribonucleosides positioned to read the codon in the mRNA. Over the years, scientists have discovered that there are more than 120 chemically different ribonucleosides in tRNA and other RNA molecules in all living organisms, from viruses all the way to humans. These modifications are added to the RNA molecule by one or more cell enzymes after the RNA is transcribed from its corresponding gene. Each organism possesses

anywhere from 25 to 50 chemically different modified ribonucleosides ranging from simply addition of a methyl (CH_3) group to very complicated chemical structures requiring 10 steps to synthesize. These chemically modified ribonucleosides are most prominently observed in tRNA.

The breakthrough that revealed the new translation scheduling mechanism occurred when researchers found that stress-reprogrammed tRNAs read codons specifically enriched in genes required to respond to that stress. The net result is selective and rapid production of the proteins coded by these stress-response genes – a kind of "just-in-time" production process geared to adapting to environmental changes.

The discovery of this tRNA modification reprogramming and codon-biased translation mechanism revealed a previously unknown property of cells that was not apparent when any single system was examined in isolation – codon biases, protein levels or tRNA modifications. By coordinating the analysis of all of these systems using the principle of big data analytics, the researchers were able to see this "transcendent" behaviour of cells under stress – critical coordination among dozens of tRNA modifications and dozens of synonymous codons. The implications are widespread, with similar systems likely in all types of cells. Since these tRNA modification enzymes are critical to the survival of bacteria that cause human infections, such as tuberculosis, the tRNA modifying enzymes could serve as targets for developing new antibiotics or new drugs that work to reverse resistance to existing antibiotics.