Taking a Crack at the Microtubule Code

Chisomo Mwale
Department of Biology
Lake Forest College
Lake Forest, Illinois 60045

The first time you heard the word “microtubules,” was probably during a high school Biology class. You were learning about DNA; how it is replicated, when your teacher discussed how fibers that form from opposite ends of the cell help align the chromosomes until they are separated. These fibers or “microtubules,” did not captivate you as much at the time because it seemed they served one purpose. After taking an introductory college-level biology course you learned that important functions within the cell aside from DNA replication. For instance, they help provide motion of the cilia in the epithelial cells that line our trachea. But have you ever wondered how exactly do they do that; why scientists are so interested in how they perform their various functions? And what could knowing more about microtubules possibly serve you and me? Scientists have found that the answer to these pressing questions may lie in the structure of the protein tubulin.

Tubulin, the major building block of microtubules, consists of two large chemical compounds α-tubulin and β-tubulin. The α-tubulin and β-tubulin polymers come together to form the non-covalent complex responsible for giving microtubules their distinct characteristics. Microtubules are able to rapidly extend and shrink their ends, creating their flexibility. In addition they possess a level of rigidity required for cellular processes involved in spindle fiber formation, cilia and platelets. The combined flexibility and rigidity of microtubules has been linked to Motor proteins and Microtubule-Associated proteins (MAPs) that alter tubulin’s properties non-covalently and post-translationally. Acetylation, phosphorylation, glutamination, glycylation and sumoylation are some of the further post-translational modifications tubulin undergoes.

Despite being a single protein, further investigations have revealed that a number of enzymes work to produce alternative versions of α- and β-tubulin, chemically modifying tubulin’s overall structure. Tubulin Tyrosine Ligase (TTL) was the first enzyme linked to the modification of tubulin. TTL re-adds tyrosine residue to α-tubulin using ATP and altering its structure. Further, scientists have demonstrated that TTL absence has been linked to death in mice as a result of disorganized neuronal pathways and its inhibition has been connected to tumorigenesis and tumor aggressiveness. But what is it about the mechanisms that create tubulin’s structure that make it so complex?

Attempts at deciphering tubulin’s structure are complicated by the more recent discovery of additional modifications to the chemical composition of microtubules. Tubulin Tyrosine Ligase-like (TTLL) enzyme has been shown to modify the microtubule structure, unlike TTL, which acts directly upon soluble tubulin. Glutamination, the addition of glutamate residues to both α- and β-tubulin, and glycylation, the addition of glycine residues to the side chains of glutamates on α- and β-tubulin, have been isolated as the most common products of the TTLL family. Thirteen TTLLs have been discovered in mammals. The TTLLs are either glutamylases or glycylases and preferentially alter either α- or β-tubulin, or both. Rather than one distinct pathway, tubulin undergoes various modifications crucial to its structure and these mechanisms were not known until recently.

So why is finding out the chemical mechanisms behind the tubulin code important to science? Microtubules play an important role in giving cells their structure. They form the assembly line that helps organelles transport substances through cells. With diseases such as Alzheimer’s and Parkinson’s, where damage occurs within cells, knowledge of the tubulin code could help scientists investigate how the cell structure is changed. This could provide insight into the pathology of such diseases and possibly lead to a cure. Yet, despite the progress already made from recent discoveries on the mechanisms of tubulin, scientists are still far from completely deciphering the tubulin code. Unveiling one mechanism opens a door to more possible pathways. Nonetheless we can still be optimistic that the information we possess will enable scientists to begin investigating the pathology of various diseases.

References:

Yu, I., Garnham, C. P., & Roll-Mecak, A. (2015). Writing and Reading the Tubulin Code. Journal Of Biological Chemistry, 290(28), 17163-17172.