What should we look at in the cell?

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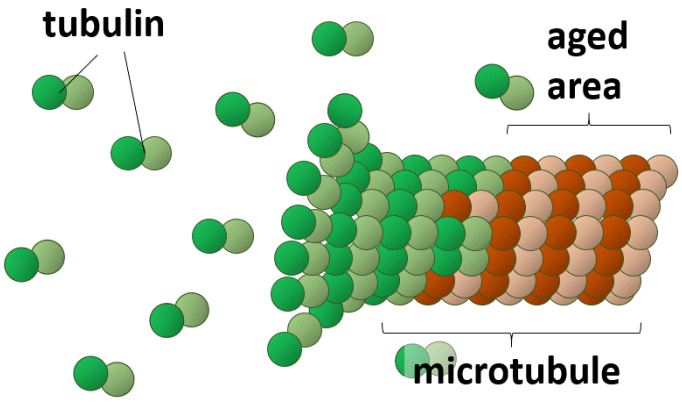

Biological phenomena, such as cell division and communication between cells, have long been considered as a collection of chemical reactions and interaction between molecules. In this point of view, biologists have been focusing mainly on the linkage of vast number of biomolecules, like which protein binds to which, or which cellular function is caused by which reaction. Recently, however, it became clear that our imagination of lives is too simple, thus in some cases, we should look at different aspect of cells. For example, possibly accumulation or shape transition of some biomolecules can be meaningful for cells. Considering this “biological information”, to what extent we should apply this way of thinking is still under research. Here, I will show in the following section a typical example about filament-like structure called “microtubule” because it is an indispensable component for many organisms from yeast to human.

Microtubules are composed of a large number of a monomer protein, tubulin, forming a tubular shape structure. Microtubules are cytoskeleton – literally, "cell's bone" – and they provide cells with mechanical strength, become "highway" for transportation in cells, and pull chromosomes apart as well upon cell division.

When you heard "skeleton", you may imagine a static structure. However, if you look at microtubules under a light microscope, you will notice that they are highly dynamic: they elongate (polymerize) or shrink (depolymerize) at the both tips all the time. This nature of microtubule, so called "dynamic instability", is due to the aging process unique to microtubule. Tubulin has two types of state: fresh state and aged state, but all the unpolymerized tubulin in the cell's solution, or cytosol, is kept fresh. After tubulin is incorporated into the body of microtubule, it gradually changes to aged state if its neighbor is in the aged state. As a result, the aged state propagates from the center of a microtubule to the tips. A microtubule continues to elongate as long as its tip is in a fresh state, but once the tip of the microtubule becomes the aged state, it stops elongating and switches to shrinking state. Dynamic instability can be considered as competition between tubulin incorporation and propagation of aging process.

Dynamic instability has long been thought to be controlled in a simple manner – the amount of microtubule in a particular region inside the cell is adjusted via

promotion/inhibition of microtubule polymerization/depolymerization by microtubule binding proteins. This picture of microtubule regulation is partly correct because many proteins were discovered to be regulators for microtubule polymerization or depolymerization rate. However, biologists have found an interesting phenomenon that cannot be explained by the simple model[1]. Let me discuss it next.

There is a protein called katanin (named after Japanese sword “katana”), that “cuts down” microtubules. It has been thought to destabilize microtubules because once a microtubule is split, aged-state tubulin region is exposed at the newly generated tips, which will cause fast depolymerization of the microtubules. To study the cellular function of katanin, biologist made a mutant cell in which katanin activity is disrupted to see if there are any phenotypic changes during its growth[2]. What do you think will happen in the cell? You may suppose that the amount of microtubule should increase because there are less katanin able to cut microtubules. However, interestingly, it conversely decreased in the cell! This means that the presence of katanin contributed to the abundance of microtubule. How could this happen?

Recently, some researches presented an elegant answer for this counterintuitive outcome. An electron microscope experiment[1] revealed that katanin does not completely cut microtubules into separate pieces: it destroys microtubules just partly, as if it digs a

hole on the microtubule surface. Unpolymerized, fresh tubulins in the solution are then spontaneously incorporated into the hole, making a “island” surrounded by aged tubulins. This turnover makes a microtubule younger, demonstrates a novel type of microtubule stabilization mechanism in the cell. Biologists found that microtubule bending and collision between microtubules also causes partial breakage in the microtubule body, and the worn-out microtubules are repaired in a similar manner mentioned above. Moreover, it was revealed that the defect itself on microtubule can be a signal for some proteins, thus recruiting them to the damaged site[3].

As can be seen from how microtubule defects work in cells, cellular machineries may also depend on or triggered by occasionally occurred physical events in an unimaginable mechanics. We should not only focus on what protein exists, where protein localizes, but should also pay more attention to some characteristic shapes and defects, because they could have important information for cells. The next generation of biology should search in more detail for what kind of “biological information” biomolecules recognize, and how those subtle differences are amplified to global changes in the cell or even a whole organism. For instance, it is known that DNA forms three-dimensional structure in the cell nucleus[4], so that some specific shapes of DNA possibly contribute to characteristic gene expression. By investigating DNA structure,

scientists could elucidate the big problem in biology, that is why cells looks totally different and expressing different set of proteins, even though they have exactly the same genetic information.

Also, we can make use of the “biological information” for novel drug development. The potential of current methods is limited because almost all the medicines work based on the old picture of biology: some block enzymatic reaction and others interrupt protein-protein interaction. In the future, we should also search for how to treat diseases by converting the shape of specific biomolecule and controlling the “biological information”. This is a promising strategy for some diseases like Alzheimer’s disease, in which a pathological form of protein is known to be one of the major causes[5]. Furthermore, this novel drug discovery method will work complementary to the existing one to cure diseases.

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