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Opinion

Microtubules: Are they the Inner Alpha-Beta of the Neuronal Machine?

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Received: February 22, 2017; **Published:** March 01, 2017

Microtubules are dynamic structures built up by αβ tubulin dimers, which carry out primary roles in a multitude of cellular functions. Some of them are common to all cell types, as the formation of mitotic spindle during the cell division, the promotion of cell migration and polarization, or the delivery of proteins and organelles; others are cell specific, as the time coordination of heart beating [1] or the stabilization of neuronal process and synapses [2]. Since microtubules alternate slow polymerizing phases to rapid shrinking ones, the fine tuning of their stability allows individual microtubules to adapt themselves to the specific and time-restricted cellular demands and is fundamental for the execution of all microtubule-based functions. The regulation of microtubule stability depends on the coordination of different, and sometimes cell-specific, factors [3]: the expression of peculiar tubulin isotypes, the occurrence of tubulin post-translational modifications and the recruitment of numerous microtubule-interacting proteins. The combination of these factors provides a potential for encoding patterns on the microtubule surface and for generating functional microtubule heterogeneity, leading to the concept of a "tubulin code". This idea relies on the existence of the "histone code", which regulates the expression of specific genes and which is, in some ways, the inner alphabet of the nucleus. Similarly, the tubulin code is important for the proceeding of most of the cell functions taking place in the cytoplasm and, thus, it could fulfil the role of the alphabet of the cellular machine. Just to make an example, it was recently demonstrated that different combinations of tubulin genes and post-translational modifications govern motor velocities, processivity and microtubule depolymerisation rates, highlighting that motor proteins recognize specific surface patterns [4], which specify the time and the place of intracellular delivery and may serve other selective functions.

All these aspects are even more important in the central nervous system, where microtubules can be implicated in the birth, in the development and in the death of a single neuron, and they seem to participate even to higher-order functions [5]. Indeed, different patterns of microtubules (in term of spatial organization and stability properties) are found in specific neuronal compartments; furthermore, these patterns change during neuronal differentiation, maturation and aging, thus influencing all aspects of neuronal life. It is largely accepted that alterations of one of the aforementioned microtubule-mediated processes likely cause nervous system abnormalities and several human neurodevelopmental disorders have been linked to mutations in various tubulin family members [6]. In recent years, it is becoming clear that the failure of the control of microtubule system can specifically affect those neuronal subpopulations whose requirements for microtubule integrity is pressing as, for example, long-projecting nigrostriatal dopaminergic neurons or various type of motor ones. Therefore, microtubule alterations can induce pathological states and direct evidences indicate that microtubules are a probable culprit and a possible therapeutic target in neurodegenerative disorders [7]. We mentioned about the birth and the death of neurons, but what's in the middle? For long time, it was supposed that the major neuronal function of microtubules was the delivery of proteins and organelles, including synaptic vesicles, to the place where they are demanded; nowadays, ever more abundant evidences confer to microtubules an active role in the neuronal functioning. Indeed, it has been proved that microtubules can invade the "actin zone" reaching the cell membrane and, thus, they directly modulate the activity of specific receptors and ion channels. Furthermore, pure microtubules seem to be able to conduct ions and current [8], even though this needs to be confirmed in neuronal cell. Surely, microtubules act as information carriers inside the cell and they have been implicated in memory formation and consolidation [9]. For this process is fundamental the ability of microtubules to sustain the formation and the stabilization of specific synapse, although their role is not limited to this action. Someone speculated that even consciousness could rely on the activity of microtubule system [10]; nevertheless, this point is highly

controversial and seems to be unlikely, at least under the light of quantum physics. Nonetheless, dysfunctions of microtubule system are observed also in diseases which imply alterations of the mental state [11], as schizophrenia. All these processes have been somehow related to subtle changes of the tubulin code and, thus, highlight how important are the microtubule patterns in carrying out both basic-cellular and higher-order neuronal functions.

It is my personal opinion that the combination of advanced and groundbreaking techniques as super-resolved and *in vivo* time-lapse microscopy, single cell transcriptomics and proteomics, maldi imaging, induced pluripotent stem cells and brain organoids, and whichever approach one could image to use, will give us the most exciting information about the real role of tubulin code in neurons, maybe revealing that it is the alphabet of the neuronal machinery. Furthermore, I will be not too surprised if, in the next years, it will become clear that neuronal subpopulations differ for the "microtubule dialect" used and thus, in a way similar to the classification based on the diverse neurotransmitters released, it could be useful having a brain atlas which defines neurons in terms of microtubule language.

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Volume 5 Issue 2 March 2017