The Civil War of the Brain

Yuliya Zayats
Department of Biology
Lake Forest College
Lake Forest, Illinois 60045

My name is Alice and in the last few moments of my life, I am experiencing tremendous trauma, both physically and emotionally. I am no longer able to function as a normal hippocampal pyramidal neuron, and I have seen my best friend wither away in anguish among millions of other brain cells. It brings me great pain to inform you that despite all the losses and battles that we have endured, we have lost the war.

It all started when I was born through a process called neurogenesis in a young girl named Melissa, nine weeks after conception from a progenitor parent cell, which came from a stem cell. Soon after my birth, I set out on a journey to find my place in this vast and wondrous human brain. My guide was a steadfastly radial glial cell that led me to my new home in the hippocampus known as the CA1 field. Upon arrival, I noticed a neurotrophic molecule called basic fibroblast growth factor, which caused me to differentiate into a neuroblast. As the new kid in the neighborhood, I made my first friend who was a neuron named Leslie who lived right next door. Thanks to Leslie I was able to make one of the most important decisions of my life and that is to become a pyramidal hippocampal neuron, as a result of the molecules she and other pyramidal neurons secreted. Cell-adhesion molecules as well as trophic molecules also helped me find my proper place by directing my growth cone to the right target cells. Because of this phenomenon, I was able to position myself near Leslie and other target cells and to form my first connections. As Melissa was born, she was exposed to many sensory stimuli, which sculpted the connections I had with other neurons. The connections that were used were often strengthened, while the connections that were rarely used were pruned. This process strengthened my bond with Leslie, who remained my dear friend for many years to come.

As Melissa grew from a toddler into a young child, the thinning of the motor cortex helped her gain better dexterity in her movement and the thickening in the left inferior frontal cortex helped her master better language comprehension. Our neighborhood encountered major changes as well. As Melissa acquired more memories over the years, including spatial, as well as long term memories, me and Leslie received input from the friendly pyramidal cells from the Schaffer collateral, and sent the information to the subiculum cortex as well as the entorhinal cortex. I can truly say Leslie and I had many delightful years together in forming and passing memories Melissa acquired throughout her childhood, adolescence and adulthood. As my fellow CA1 pyramidal cells and I aged, some of us passed away and others lost MDA receptors, which made it more difficult for Melissa to remember and learn new information. This is all typical in an aging brain; however, in Melissa’s early sixties Leslie and I noticed a peculiar β-amyloid peptide, which is derived from the β-amyloid precursor protein located in our outer cell membrane. This suspicious peptide looked very strange to us because it had a 42 amino acid sequence instead of the usual 40 amino acid sequence, which was cut by beta- and gamma-secretase. We did not know what the cause or purpose of these polypeptides was, but other cells in the CA3 region of the hippocampus appeared to be in a state of alarm.

A few weeks later, I found Leslie screaming in pain, with her body riddled with putrid black helical filaments. I asked what was wrong, and she replied that her microtubules were ruined. Because she was unable to transport vital molecules and organelles throughout her body, it was difficult for her to maintain the shape of her cell body. Meanwhile, the A-beta peptides began to cling to one another forming long filaments that made it extremely difficult for me to communicate with other neurons. However, the few signals that I could receive I found quite frightening because I was informed that the ventricles within the brain were expanding and my neuron brothers and sisters were dying at an alarming rate. Among all this mayhem, the armies of microglial cells came rushing to our aid and began phagocytosing the β-amyloid plaques that seemed ubiquitous. I was horrified and bewildered at this chain of events, until it finally dawned on me that the brain was in a civil war, being killed by its own misfolded proteins. In the meantime, Melissa had been experiencing the same amount of distress as we had. She had lost the memories of her loved ones, along with her ability to plan and reason properly. She also found it difficult to find words for objects and underwent personality changes. Melissa’s family consulted her doctor and decided it would be best for her to try a treatment that involved vaccination against β-amyloid plaques. The vaccination elicited passive immunization in Melissa’s body through the use of premade antibodies. Injected antibodies eliminated A-Beta in the rest of the body, which caused a concentration gradient that transferred A-Beta from the brain to other parts of the body. The treatment slowed down the accumulation of β-amyloid plaques in some parts of the brain; however, not much could be done to permanently stop the merciless attacks of the misfolded proteins, because the problem lay deep within our DNA. You see, our own genetic code contained a mutation in presenilin that changed the structural composition of the A-beta portion of the Amyloid precursor protein. This alteration made the Amyloid precursor protein more prone to producing toxic A-beta protein, which tends to clump together because of its water-repelling properties.

A-beta plaques, along with the black tau tangles, have already obliterated Leslie’s body and slowly began pervading through every part of mine. I watched her vitality fade away slowly along with Melissa’s memories, and waited for the microglial cell to pick up the remnants of her axon, cell body and dendrites. I acknowledged that the end was near and I made a decision to accept my approaching death and that nothing could be done to reverse this malady. Although we might have lost the war, hope still prevails in the scientific research done on Alzheimer’s disease throughout the whole world. I can only hope that one day the brain will not be a victim of its own proteins.

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