New Developments in MS Research, a monthly column

by Farren Briggs

MS Researchers Identify New Biological Mechanisms Regulating IL7R Expression

Our immune system is comprised of many different cells that are the great guardians of our bodies – protecting us from invading pathogens, and removing infected and malignant cells, while overlooking healthy cells. This defense system is coordinated through precise but dynamic signaling of various proteins and receptors. In multiple sclerosis (MS) and other autoimmune disorders, there is a disruption to the cellular symphony, leading some immune cells (e.g. T cells) to mutiny and attack healthy tissues. A prominent source of this disruption results from an above average burden of common genetic alterations (variants occurring in at least 5% of a population) in genes involved in the immune system.

Our genes are the units of heredity that make up our unique biology. In the same way that they determine the color of our eyes or the shape of our nose, genes can determine our vulnerability to disease. One of the earliest genes associated with the onset of MS is *IL7R*, which encodes the interleukin-7 receptor (IL7R) essential for survival, proliferation, and maintenance of T cells. IL7R can be found on the surface of immune cells or freely floating throughout the body, however a genetic variant that shifts the balance from the surface-bound subtype to the free floating subtype has been confirmed to increase one's risk for MS. This month, two studies were published investigating additional mechanisms that contribute to this shift in IL7R subtypes.

The first study by Galarza-Muñoz and team was published in Cell [1]. I was fortunate to be a part of this multidisciplinary approach to identifying other genes that contribute to the shift in IL7R subtypes. We conducted two experiments simultaneously. The first experiment was carried out in two cell models, where the influence of 89 different proteins on IL7R synthesis was investigated. The absence of an enzyme, DDX39B, involved in assembling proteins from genes, was shown to dramatically favor the shift of IL7R subtypes to the free floating variety. The second experiment, which I conducted, was a statistical analysis of genetic data from over

4,088 individuals with MS and 7,444 unaffected individuals. Due to the large number of individuals who were willing to share their genetic data, I was able to detect a significant statistical interaction between the *IL7R* variant and a variant in *DDX39B*. Individuals with the interacting IL7R and DDX39B variants, were almost three times more likely to have MS than those without these two alterations. Thus, both experiments independently implicated DDX39B as shifting the balance of IL7R subtypes and increasing risk for MS. They also highlight the value to scientists of ordinary people's willingness to share biological samples and data about themselves. This is true for people with MS, as well as for others who can serve as "healthy controls."

The second study by Bina and team was published in Neuroscience Letters [2]. The majority of our DNA does not encode a protein, and for many years scientists thought the non-protein coding regions were "junk DNA." However, within the past decade various patterns have been detected in our "junk DNA." Some of these patterns include genes encoding non-protein molecules (examples of these are called long non-coding [lnc] RNAs) that facilitate or disrupt actual protein synthesis. In 2014, a gene encoding a lnc RNA was detected near the *IL7R* gene, and was shown to influence the expression of IL7R protein – and thus named *lnc-IL-7R*. Bina and team conducted an exploratory analysis to compare the level of lnc-IL-7R and IL7R subtypes in blood from 36 individuals with MS and 30 unaffected individuals. Higher levels of lnc-IL-7R was statistically associated with lower levels of both IL7R subtypes, but more so for the surface-bound subtype. There was also preliminary evidence demonstrating that IL7R subtype patterns were associated with age and gender, and the length of time an individual had MS – suggesting a role for IL7R disruption in the progression of MS.

Collectively, these studies suggest multiple independent mechanisms regulating IL7R expression, and that IL7R may contribute to MS progression. By understanding how the immune system goes awry and by shedding light on biological mechanisms predisposing individuals to contract MS, we researchers hope to help improve the time to and accuracy of a MS diagnosis, and to positively contribute to the greater knowledge needed to develop novel therapies.

1. http://www.cell.com/cell/abstract/S0092-8674(17)30286-6
2. http://www.sciencedirect.com/science/article/pii/S0304394017300940