Journal of Clinical Immunology (2020) 40:789–790
https://doi.org/10.1007/s10875-020-00837-z

COMMENTARY

Bourgeoning Scientific Research in Down Syndrome

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Received: 20 July 2020 / Accepted: 22 July 2020 / Published online: 25 July 2020

The earliest evidence of existence of individuals with Down syndrome (DS) dates to ancient art in Mesoamerica. Furthermore, analysis of bone structure from graves in France, California, and Ireland suggests that individuals with DS were part of our societies for millennia. In more modern medical terms, DS was described in the mid-1800s by scientists in France and England [1, 2]. A century later, in 1959, the genetic underpinning was described leading to now the synonymous term trisomy 21 (although the genetics of DS can be substantially more complex) [3]. Either way, tremendous progress has been made over the last half a century in the medical treatment of individuals with DS. The life expectancy for individuals with DS went from about 30 years in the 1980s to about 60 years in 2020 [4]. But there is much more we can, should, and actually are doing to understand physiology of individuals with DS. In this issue of *JoCI*, a review article and a research article are dedicated to immunology in individuals with DS.

Verstegen and Kusters review the literature on documented immune disbalance in DS, in particular in the adaptive immune system [5]. They point to inborn defects in thymic function, and the ensuing disbalance in T and B cell development. It appears that lower levels of B cells and T cells in DS when compared with age-matched controls are common trend, with different subsets being disproportionately affected. Worth noting is that the conflicting reports do exist on particular T cell subsets (i.e., T regs), and thus more detailed work is needed to document the adaptive immune dysregulation at all ages in Down syndrome. Perhaps worth further exploring are the T cell receptors and B cell receptor repertoire specificities as the technology has evolved.

Also in this issue, Kong et al. elegantly show that the cluster of genes encoding type I IFN receptor, one subunit of type II IFN receptor, and one subunit of type III IFN receptor contribute to mild hyperactivity of the respective pathways [6], which is in line with the previous reports [7, 8]. Interestingly, Kong et al. note that only 12% of individuals with DS have detectably increased levels of circulating type I IFN cytokine, but most have increased levels of ISGs in peripheral blood. This may suggest presence of the cytokine in IFN silos, a mechanism of cytokine intracellular retention which was recently reported [9]. Alternatively, a different mechanism whereby the feed-forward loop of type I IFN production is regulated by the very increase of type I IFN signaling should be assessed.

The discovery of physiology governing cytokine production and responses in individuals with DS has started and is poised to advance the field substantially in the coming years. These discoveries will be crucial to improving the clinical manifestations of the dysregulated immune system in DS, from the increased incidence of autoimmune diseases to the susceptibility to infections [4]. This is particularly relevant given that we are in the midst of a global SARS-CoV2 pandemic which may disproportionately affect individuals with DS [10].

Our goal is to improve quality of life, and ultimately completely resolve symptoms in DS. It is our societal duty to advocate for and dedicate to what rightfully appears to be a burgeoning era in scientific understanding of Down syndrome. If we slow down even a tad, we will have failed individuals with DS and ourselves as well. Recent push by the NIH and the private donors to support the scientific discovery in DS is truly a promising path to leave behind us the unconscious ableism in scientific discovery in DS.

Summary of Significance of the Paper Being Editorialized to Readership New era of scientific discovery governing

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pathophysiology in Down syndrome is underway. A review and a research article in this issue of JoCI showcase this progress.

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