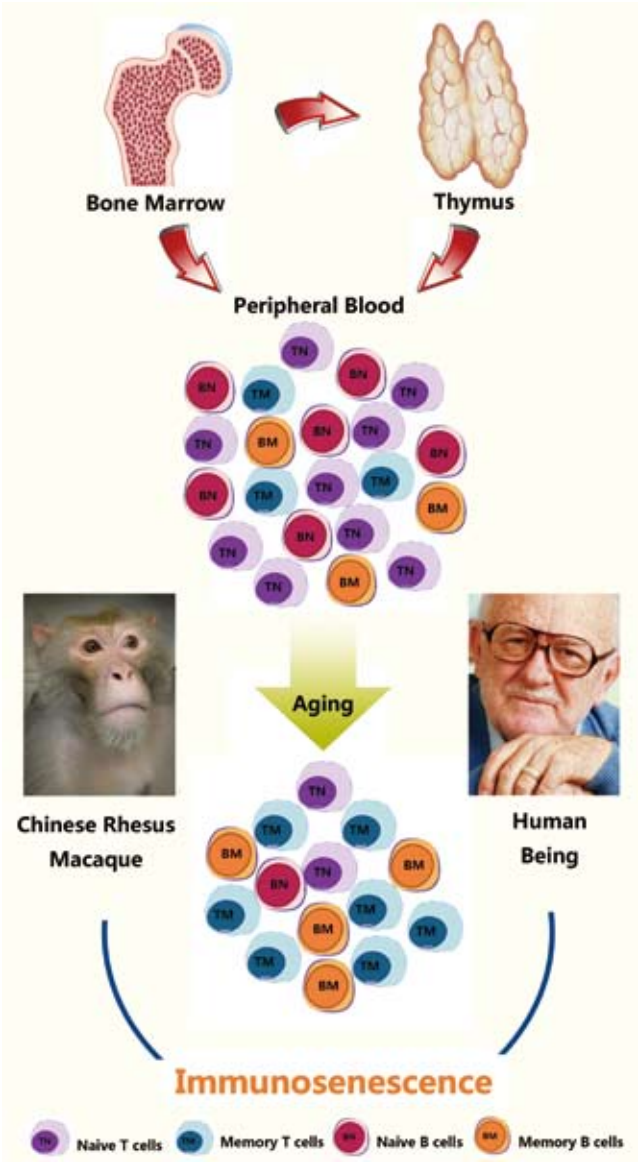
Of Monkeys and Men: New Insights into Using Chinese Rhesus Macaque as a Viable Model of Human Aging

Of all human conditions, aging and death are perhaps the most universal. Unfortunately death among elderly populations is often a drawn out and painful affair, as advanced age is accompanied by marked rises in morbidity and mortality due to infectious diseases. Precisely why this is the case has been subject to a great deal of speculation, but one commonly held explanation is referred to as immunosenescence, where the human body undergoes a remodeling of both innate and adaptive immune responses, and some functions are enhanced while others diminished. Both responses are key to the human immune systems, which fights off outside pathogens. The innate immune system serves as a first line of defense, while adaptive immunity functions by actively fighting off pathogens that have made it past the innate system.

As humans age, both systems undergo marked changes. Several different explanations have suggested that as the body ages, the innate immune system is compromised by compounded defects in the activities and functions of neutrophils, monocytes/macrophages, dendritic (DCs) and natural killer (NK) cells, and increased permeability of mucosal barriers leave the elderly at greater risk of becoming infected, and more susceptible to further infections. The adaptive immune system undergoes more interesting and profound changes, likely due to the involution of the thymus, one of the primary lymphoid organs and the site at which T lymphocytes mature. Due to the nature of the thymus, as humans age, they begin to lose naïve T cells. Concurrently, there is an increasing accumulation of memory subset of T cells, particularly highly differentiated effector memory $CD8^+$ T cells, leaving a marked imbalance of the CD4/CD8 ratio. Other changes, such as a decreased number of B cells, and a significant reduction in T cell and B cell repertoire diversities. Ultimately, these changes to the adaptive immune system can shape at an "immune risk profile"



Similar immunosenescence progression in ChRM and human

that has served as a functional predictor of mortality or longevity.

While some research has been done to investigate the general nature and broad effects of immunosenescence, studies on human populations are not always viable. Traditionally, researchers have used rodent models to study, but these models are rather limited to study aging, as they are not nearly as long-lived as humans or other primates, and they are more genetically distant to humans. Alternatively, ZHENG Yongtang's team at the Kunming Institute of Zoology proposed that using the Chinese rhesus macaque, a long-lived species of non-human primates that shares greater genetic and physiological similarities with humans, would be far more ideal.

ZHENG's team noted that a variety of studies previously found that rhesus macaques can serve as robust translational models of many human diseases, especially for age-related changes or alterations in the immune system. In older macaques, the changes to both the innate and adaptive immune systems that are described by immunosenescence are quite similar to those seen in humans, while studies on rhesus macaques infected with simian immunodeficiency virus (SIV) closely mimic the pathology of human HIV/AIDS infection. Aging and HIV disease progression share many features, including naïve T cell depletion, decreased CD28 expression on $CD8^+$ T cells, and accelerated thymic involution, suggesting that macaques may be a valuable model for aging research, but there are large gaps in the existing literature on the features of immunosenescence in non-human primates, and especially in the aging populations.

To extend fill the void on research into aging in non-human primates, ZHENG's team designed a cross-sectional experiment to age-related changes in circulating T cells and B cells. Using Chinese rhesus macaques between two and 24 years of age, ZHENG's team noticed a strong similarity between the aged macaques and humans, including decreased CD4/CD8 ratio, a loss of naïve T cells, a marked reduction in B cells and increased levels of PD-1 expression in T cells and CD95 expression in B cells. Curiously, they also found that the effects of T cell aging were somewhat sex-specific, with older rhesus males having a more rapid loss of $CD4^+$ T cells and naïve T cells and consequently a more severe immune risk profile. The same is largely true of humans; worldwide, despite advanced medical care and standards of living, women still tend to outlive men and have longer life expectancies.

Ultimately, ZHENG's team found that Chinese rhesus macaques share a significant homology with humans, making them an ideal animal model for further targeted studies on aging, as well as on the study of immune system disorders. Ideally, further uses of rhesus macaques may help researchers gain a much clearer understanding into how aging and the concurrent changes in immune responses operate in humans, opening the door for future research and the possible development of ground-breaking longevity treatments.

(Text by Andrew Willden)