BIOINFO 2025]

Immune dysregulation and aberrant B cell responses drive age-dependent severity in SFTSV infection

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Aging significantly alters host immune responses to viral infections, including Severe Fever with Thrombocytopenia Syndrome Virus (SFTSV), which is associated with particularly high mortality among elderly individuals. Despite its substantial fatality rate and pandemic risk, no effective treatments are currently available, and the mechanisms by which aging shapes SFTSV pathogenesis remain poorly defined. To investigate this, we utilized an immunocompetent ferret model that closely recapitulates human SFTSV infection and performed multi-tissue single-cell RNA sequencing in combination with histopathological assessment. Our analyses demonstrated that, following SFTSV infection, aged ferrets undergo pronounced decrease of critical immune cells (most particularly B and T cells) driven by virus-induced cell death and excessive hemophagocytosis in hematopoietic organs. In contrast, young-adult ferrets rapidly clear the virus with minimal lymphocyte perturbation. Notably, aged ferrets further exhibit striking immune dysregulation, including aberrant activation of T-bet$^+$ age-associated memory B cells (*T-bet*$^+$ ABCs) and expansion of dysfunctional plasmablasts (*MKI67*$^+$ PB1), which act as major viral reservoirs promoting systemic viral dissemination. Comparative analysis confirmed that the *MKI67*$^+$ PB1 cells constitute the predominant SFTSV-infected cells in both aged ferrets and human fatal cases, harboring the highest viral loads per cell. Moreover, monocytes and macrophages in aged ferrets display heightened inflammatory gene expression, contributing to the hyper-inflammatory milieu during infection. Together, these findings underscore that dysregulated memory B cell responses and hyper-inflammation are critical drivers of age-dependent SFTSV pathogenesis, offering potential targets for therapeutic interventions in elderly populations.