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LETTER TO THE EDITOR

Accelerated T-cell exhaustion: its pathogenesis and potentially severe outcomes

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Several cancers and intracellular pathogens subvert immune defenses using proteins and short non-coding ribonucleic acids (RNAs) [1]. Non-coding RNAs can bind to host cell signal transducer and activator of transcription (STAT) transcription factors and messenger RNAs to disrupt gene expression of interferon-stimulated genes (ISG) and messenger RNA processing, enabling pathogens to evade immune cells including natural killer cells (NK-cells), thymic cells (T-cells) and bone marrow cells (B-cells) [1]. Furthermore, ISG disruption could disrupt ISG cellular defenses targeting other pathogens within the host cell.

T-cell exhaustion inhibits T-cell functions for $CD4^+$ and/or $CD8^+$ T-cells, and results from chronic infections producing continuous antigens [2, 3]. T-cell exhaustion comprises T-cell metabolic exhaustion and mitochondrial dysfunctions, reduced proliferation and effector functions, and potentially diminished T-cell numbers [3].

T-cell exhaustion inhibits $CD4^+$ and $CD8^+$ T-cell reactions to pathogen infections [3]. T-cell inhibitory receptors participate in T-cell exhaustion, including the programmed cell death protein 1 (PD-1) and lymphocyte activation gene 3 protein (LAG-3) [2, 3].

However, inhibitory receptors are also expressed during T-cell differentiation or activation, and their presence during active infections doesn't necessarily indicate T-cell exhaustion [4]. Furthermore, during acute infections, certain cytokines can increase T-cell expression of inhibitory receptors within 24 h, and substantially increase expression within 48–72 h [4].

How can T-cell exhaustion in antigen-specific T-cells impair T-cells targeting other pathogens? A chronic first pathogen infection can accelerate T-cell exhaustion for a second pathogen using cytokines causing T-cell inhibitory receptor (e.g., PD-1) expressions, and by inducing infected cells to express inhibitory ligands (e.g., PD-L1) for those inhibitory receptors [2]. A second pathogen infection can utilize the infected cell's expressed inhibitory ligands to accelerate exhaustion of T-cells targeting the second pathogen. This could potentially enable the second pathogen to overcome the host's immune defenses [2]. This could be dangerous in novel infections where antibodies (produced from B-cells by $CD4^+$ T-cell assistance) are numerically insufficient and/or inadequate in affinity selection/maturation from somatic hypermutation to suppress the second pathogen [5]. Mortality could occur, where the second pathogen infection induces accelerated T-cell exhaustion and the second pathogen overwhelms the host's immune system.

In murine T-cell exhaustion, if antigen exposure from lymphocytic choriomeningitis virus (LCMV) is continuous, T-cell exhaustion first appears at about two weeks post-infection and an irreversible complete T-cell exhaustion phenotype is seen approximately four weeks post-infection [3]. If it is plausibly assumed that other viruses in mice or humans have approximately the same timing regarding conventional T-cell exhaustion, and infection mortality is approximately contemporaneous with completely developed T-cell exhaustion, COVID-19 pandemic mortality timing statistics might discern between conventional and accelerated T-cell exhaustion fatalities [6].

$CD8^+$ and $CD4^+$ T-cell exhaustion participates in COVID-19 mortality [6]. Exhaustion can also affect follicular helper $CD4^+$ T-cells, in lymph node and spleen germinal centers, essential for antibody affinity maturation, isotype switching, generation of memory B-cells, and B-cell

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differentiation into immunoglobulin (antibody) secreting plasma cells [7]. Accelerated T-cell exhaustion could be lethal in first-time infections by the second pathogen, if germinal center follicular helper $CD4^+$ T-cells are inhibited, causing immunoglobulin/antibody B-cell expressions to lack optimal immunoglobulin/antibody isotype switching and impair immunoglobulin/antibody improvements by somatic hypermutation and affinity selection/maturation to better target the second pathogen [5]. Patients experiencing severe COVID-19 express higher proportions of less-developed IgM immunoglobulins, compared to control or mild COVID-19 patient immunoglobulin expressions [7]. This suggests follicular helper $CD4^+$ T-cell exhaustion contributes to severe COVID-19 cases and mortalities [5, 7].

If conventional or accelerated T-cell exhaustion cause COVID-19 mortalities, the timings for conventional T-cell exhaustion, accelerated T-cell exhaustion and patient mortality are relevant. Statistical analysis of 8873 COVID-19 patient mortality cases calculated a median time from COVID-19 symptoms/diagnosis to death (16.33 days for male patients and 17.67 days for female patients), including cases primarily of Alpha through Delta variants of SARS-CoV-2 [8].

A significant difference in the time required for complete T-cell exhaustion induced by the viral pathogens SARS-CoV-2 or LCMV is possible. However, T-cell exhaustion induced by SARS-CoV-2 or other viral pathogens should have approximately equal timing, since the timing depends on the T-cells and host cells, including the times required for T-cell inhibitory receptor expression and for infected host cell expressions of inhibitory ligands. In murine LCMV infections, T-cell exhaustion characteristics first appear ~ 15 days post-infection and irreversible complete T-cell exhaustion characteristics appear at ~ 30 days [9].

Comparing the times from symptoms/diagnosis of COVID-19 to death is possible, using an adjustment factor for the delay from infection to symptoms/diagnosis. One study determined the incubation period for COVID-19, defined as the time from exposure (infection) to the appearance of COVID-19 symptoms, for the SARS-CoV-2 Alpha, Beta, Delta, and Omicron variants [10]. The mean incubation period of COVID-19 ranged from five days for the Alpha variant to 3.42 days for the Omicron variant [10]. Subtracting five days as a conservative delay after exposure for any variant of SARS-CoV-2 to produce COVID-19 symptoms/diagnosis suggests that conventional complete T-cell exhaustion appears ~ 25 days after symptoms/diagnosis of COVID-19.

Although patient co-infections and comorbidities could cause several COVID-19 mortalities and cause statistical shifts, the median times (~ 16 to ~ 18 days) from COVID-19 symptoms/diagnosis to death remain puzzling, because these times are less than the expected ~ 25 days for conventional complete T-cell exhaustion, plausibly contemporaneous with death.

Accelerated T-cell exhaustion is one plausible explanation for the median times of ~ 16 to ~ 18 days for fatalities due to the SARS-CoV-2 Alpha through Delta variants [8], instead of the expected ~ 25 days. Thus, accelerated T-cell exhaustion could be more plausible than conventional T-cell exhaustion for ~ 50% of COVID-19 patient fatalities.

In conclusion, intracellular pathogen interactions could enable accelerated T-cell exhaustion for a second pathogen. Acceleration of T-cell exhaustion is facilitated when the first and second pathogens infect the same cells, allowing reuse of the already expressed inhibitory ligands of the infected cells. The total time for T-cell exhaustion may be the shorter time required for T-cells targeting the second pathogen to express inhibitory receptors. Accelerated T-cell exhaustion, and possibly contributing B-cell dysfunctions, could explain significant mortality rates for some epidemics, including COVID-19, when host immune system defenses are overwhelmed.

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