In this theoretical paper, the author from the United States discusses possible interactions between intracellular pathogens, such as viruses, bacteria, fungi, and protozoan parasites when they concurrently infect the same host cells, and how concurrent intracellular pathogens can lead to T-cell exhaustion and subvert immune defense with potentially severe consequences.

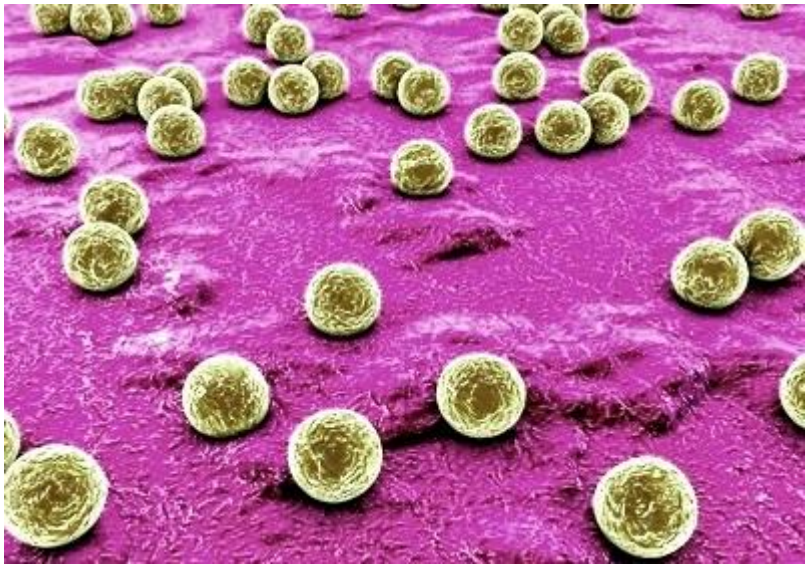
Concurrent infection with two different pathogens and accelerated T-cell exhaustion

The researcher emphasizes that chronic or latent infection of prolonged duration with the first pathogen can create a cytokine environment where T-cells express multiple inhibitory receptors. At the same time, the infected cells express multiple inhibitory ligands for those inhibitory receptors. The author gives an example of chronic infection with the parasitic protozoan *Toxoplasma gondii*. This infection increases the number of inhibitory programmed death 1 (PD-1) receptors on T-cells and at the same time, the number of PD-ligands on cells infected with *Toxoplasma gondii*. The increased number of inhibitory PD-1 receptors on T-cells and their ligands on infected cells facilitates their binding and subsequent activation.

In this situation when T-cells express multiple inhibitory receptors, and cells infected with the first pathogen express multiple inhibitory ligands for those inhibitory receptors, a novel infection with the second pathogen, especially with a virulent pathogen that creates large antigen titer, could enable the second pathogen to induce accelerated T-cell exhaustion and overwhelm a host's remaining adaptive immune system defenses.

Furthermore, concurrent intracellular infection enables the second pathogen, possibly one that produces large antigen titer, to reuse inhibitory ligands for inhibitory receptors (such as PD-L1), that have already been expressed on the same host cells. The reusing of the inhibitory ligands by the second pathogen is facilitated because the inhibitory ligands are already extensively expressed on host cells infected with the first pathogen. The reusing of inhibitory ligands for inhibitory receptors accelerates the T-cell exhaustion towards the second pathogen, thereby enabling the second pathogen to overcome the host's adaptive immune responses.

For example, the first pathogen is a protozoan parasite or bacteria, and the second is a virulent virus that can infect the same host cells already infected by the first pathogen. When the viral infection produces a high antigen titer, the accelerated exhaustion of T-cells may result in a high mortality rate.



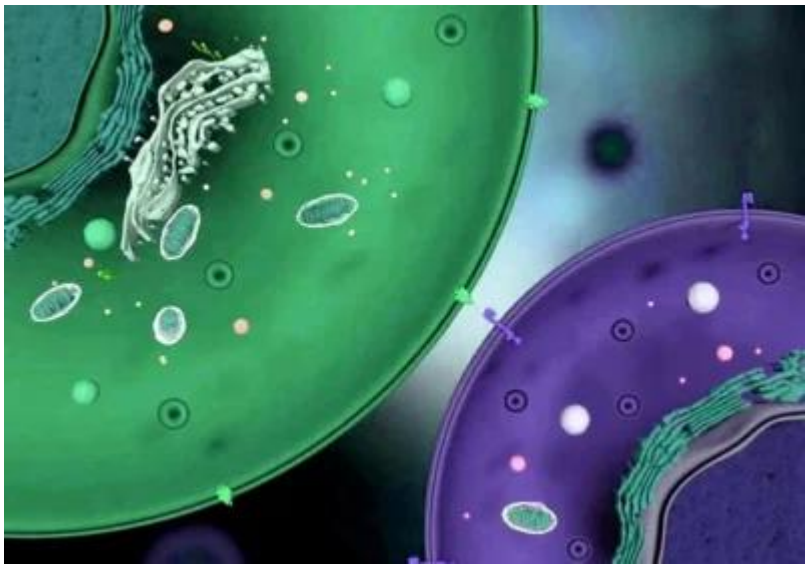
The accelerated T-cell exhaustion could be particularly dangerous in the infection with an immunologically novel second pathogen if the follicular helper CD4+ T-cells from germinal centers are suppressed. As these cells are critical for the maturation of antibody affinity, isotype switching, generation of memory B-cells, and differentiation of B-cells into immunoglobulin (antibody) secreting plasma cells, their suppression leads to inadequate number and/or selection/maturation of antibodies which should control the second pathogen.

A determination of a delay time for the second pathogen to achieve T-cell exhaustion can be based on the following: 1. the time required for host cells infected by the second pathogen to express inhibitory ligands, if they are not already expressed, and 2. the time required for T-cells to express several inhibitory receptors.

The author also discusses numerous pathways for T-cell exhaustion and/or T-cell suppression, shared by the first and second pathogens, including cytokines (IL-10, transforming growth factor-β (TGF-β), type I interferons α and β) and cells that impair T-cell functionality. Regulatory T-cells (TREG cells) also play a role in the exhaustion and/or suppression of T cells by secreting inhibitory cytokines like IL-10, interleukin-35, and TGF-β.

The author also noted that T-cell exhaustion was observed in severe cases of COVID-19, which could be the fundamental driver of COVID-19 mortality. T-cell exhaustion can affect CD8+ T-cells and CD4+ T-cells, and follicular helper CD4+ T-cells, mainly in germinal centers in the lymph nodes and spleen. As a prolonged period of lymphocyte exhaustion for T-cells and NK-cells was observed in COVID-19 survivors for months after the infection, the

author proposed that multiple lymphocyte exhaustion could be a major cause of symptoms collectively known as long COVID.



The first pathogen (latent) is a threat after T-cell exhaustion towards the second pathogen

If the host can survive the accelerated T-cell exhaustion towards the second pathogen, and accelerated second pathogen infection due to the weakened T-cell functionality, the first pathogen could become a threat. If the first pathogen is latent, T-cell exhaustion induced by the second pathogen may enable a reactivation of the latent first pathogen, with potentially severe consequences. The reactivation of a latent first pathogen, for example, *Toxoplasma gondii*, can lead to encephalitis, hepatitis, or myocarditis. This is also illustrated by the interaction between human immunodeficiency virus (HIV) and *Mycobacterium tuberculosis*. It is estimated that one-third of global HIV mortality is due to the reactivation of *Mycobacterium tuberculosis*, triggered by HIV. *Mycobacterium tuberculosis* causes more than 85 % of pericardial effusions in HIV-infected individuals. On the other side, HIV alters the natural history and outcome of tuberculous pericarditis, making HIV-associated tuberculosis a more aggressive disease with more severe myocardial involvement. Importantly, it is assumed that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can cause the reactivation of latent tuberculosis.
https://discovermednews.com/tuberculous-pericarditis-in-covid-19/

Conclusion

This theoretical article discusses possible interactions between different intracellular

pathogens (viruses, bacteria, fungi, and protozoan parasites) when they concurrently infect the same host cells. The author also analyzed how concurrent infection can lead to T-cell exhaustion and subvert immune defense, and mechanisms by which intracellular pathogens subvert innate and adaptive immune defenses.

In conclusion, pre-existing inflammation and cytokine environment created by the first pathogen could enable the second pathogen to induce accelerated T-cell exhaustion and overwhelm a host's remaining adaptive immune system defenses.

This article was published in Heliyon.

Journal Reference

Roe K. Concurrent infections of cells by two pathogens can enable a reactivation of the first pathogen and the second pathogen's accelerated T-cell exhaustion. Heliyon 8 (2022) e11371 https://doi.org/10.1016/j.heliyon.2022.e11371