Antibody for Preventing/Treating Secondary Respiratory Infections

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Overview

A novel method of preventing secondary infections, by inhibition of membrane type I matrix-metalloproteinase-1, which reduces degradation of the extra cellular matrix.

Background and Unmet Need

Pathogens that infect the respiratory system are the cause of some of the most dangerous infections, especially for vulnerable populations such as children and seniors. This is due to the host immune response which can damage the lung tissue, serving as a prime target for secondary infections. Consequently, there is a need for a method that provides better control over inflammatory response, and reduces tissue damage caused by a host immune response to an infection.

Paradigm-shifting research by the group of Prof. Irit Sagi uses an innovative method to prevent secondary infections by retaining tissue integrity. Prof. Sagiâ€™s research team has discovered that by specifically inhibiting membrane type I matrix-metalloproteinase-1 (MT1-MMP) they can limit tissue damage to the lungs of mice. Subsequently, this helps prevent secondary infections, thereby improving overall survival rates.

The Solution

Researchers from the group of Prof. Irit Sagi have discovered a unique method for treating an influenza infection, thereby reducing tissue damage and preventing secondary infections. The group inhibited membrane type I matrix-metalloproteinase-1 (MT1-MMP) to effectively stop an excessive immune response

Technology Essence

The researchers initially focused on the gene expression in lung tissue of mice after a primary infection associated with influenza. They observed a global change in gene expression and a general increase in the transcription of MMPs, specifically MT1-MMP. Furthermore, the results showed a co-localization of MT1-MMP and infected cells. Additional experiments compared the morphology of healthy and infected mice lungs, showing a significant change in the morphology of the ECM, thereby indicating substantial damage to the tissue.

Further experimental data led to the discovery of an alternative, innovative method for treating influenza infection and preventing possible secondary infections. Rather than focusing on the traditional method of targeting the pathogen, Prof. Sagiâ€™s team focused on retaining tissue integrity by reducing ECM degradation via inhibition of MT1-MMP. The group tested this by creating an assay whereby mice were initially infected with influenza as a primary infection, and four days later a secondary infection was induced by the introduction of S. pneumoniae.

The experiment was performed in two modes: preventative (A) and therapeutic (B). In the preventative mode, Tamiflu and an anti-MT1-MMP antibody were administered prior to the influenza infection. In the therapeutic mode these treatments were given after the primary influenza infection but before the secondary S. pneumoniae infection. The results in the figure below show that the most effective treatment is the combination of Tamiflu and the anti-MT1-MMP antibody in terms of survival. However, Tamiflu on its own is effective only as a preventative measure, while the anti-MT1-MMP antibody showed a general survival improvement in both modes.

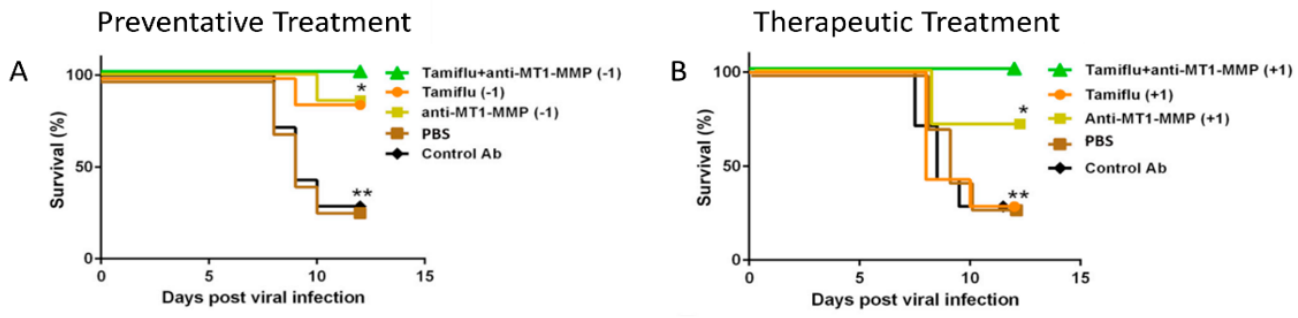

Figure 1: Comparing and combining anti-viral treatment with MT1-MMP inhibition to determine effect on mouse survival. A) Mice were treated prophylactically with Tamiflu and/or anti-MT1-MMP antibody one day prior to initial influenza infection; Four days later the mice were infected with a secondary pathogen, S. pneumoniae. B) Mice were treated therapeutically; infected initially with influenza; 24h later were treated with Tamiflu and/or anti-MT1-MMP antibody; and four days after initial infection were infected with a secondary infection with S. pneumoniae. (Mantel-Cox test applied to the Kaplan-Meier survival data). (Talmi-Frank D. et al. 2016)

Applications and Advantages

- Limiting tissue damage for the prevention and treatment of influenza and potentially COVID19.
- Novel mechanism â€“ targeting MT1-MMP to limit inflammation due to an immune response, rather than targeting the pathogen directly.
- Usage of an antibody for prophylaxis or treatment
- Synergism â€“ possibly combined with an anti-pathogen agent to assist in treatment.
- Better outcomes â€“ reduction of tissue damage and inhibition of secondary infections improves overall survival rates.

Development Status

The research team of Prof. Irit Sagi have shown a novel mechanism of treating and preventing secondary infections by inhibition of MT1-MMP. The team used mice as an infection model. They performed in vitro experiments on extracted mice lungs to characterize MT1-MMPâ€™s role in the infection pathology. They also calculated survival rates following both primary and secondary infections of mice, with and without inhibition of MT1-MMP

References

Talmi-Frank D. et al. Cell Host & Microbe 20, 458â€“470, October 12, 2016

Patent Status

USA Granted: 11,400,156 USA Granted: 10,610,588