Abstract

Acid sphingomyelinase and ceramide modulate several aspects of T lymphocyte activation. T lymphocytes are the vital players in adaptive immune response against invading pathogens. Tuberculosis is one of the most common infectious diseases, still imposing a huge death toll every year.

This project investigates the role of acid sphingomyelinase in tuberculosis-specific peptide25 T cell receptor (TCR) transgenic CD4+ T cells, murine primary lymphocytes and human Jurkat cells.

Data reveals that pharmacological inhibition of acid sphingomyelinase by Imipramine significantly impairs the activation of several TCR signaling kinases, however genetic deficiency of acid sphingomyelinase only shows limited effects. Moreover, examination of peptide25-induced activation of TCR transgenic CD4+ T cells demonstrates that Imipramine significantly inhibits the late activation events, i.e., proliferation, differentiation, cytokine production and induces cell death following stimulation due to ineffective initial activation. In contrast, acid sphingomyelinase-deficient transgenic (P25/Asm$^{-/-}$) CD4+ T cells present very similar responses regarding the late activation events, compared to wild-type control cells (P25/Asm$^{+/+}$). In parallel, systemic infection of wild-type and acid sphingomyelinase-deficient mice with Bacillus Calmette-Guerin, which is a live attenuated form of *Mycobacterium bovis* with a similar antigenic profile to *Mycobacterium tuberculosis*, reveals the insignificant function of acid sphingomyelinase in both CD4+ and CD8+ T cell activation *in vivo*. In addition, mass spectrometry analysis of lipid composition of Jurkat cells following Imipramine treatment reveals a diminished level of sphingosine and sphingosine-1-phosphate. This indicates that the inhibitory effects of Imipramine in T cell signaling and late activation events might not be entirely due to the inhibition of acid sphingomyelinase but also acid ceramidase. Thus, this project gives some new insights into the role of acid sphingomyelinase in T lymphocyte activation.