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Bacterial Capnine Blocks Transcription of Human Antimicrobial Peptides

The US CDC believes that 65% of all infections in developed countries may be caused by pathogens in biofilms. Electron Microscopy has shown that these bacterial communities can evade phagocytosis, and persist in the cytoplasm of monocytes, macrophages, lymphocytes and neutrophils. Three decades ago, Wirostko, et al, found such intraphagocytic communities in Crohn's disease, Juvenile Rheumatoid Arthritis and Sarcoidosis [1]. However, the mechanism(s) by which such persistent bacteria could evade the immune system have remained elusive. Recently,16S RNA from species of gliding bacteria never thought to be able to survive in-vivo, have been found in surgically removed biofilms [2]. This study set out to identify whether the genomes of these gliding bacteria might yield insight into mechanisms by which such persistent pathogens could evade phagocytosis.
METHODS: A single Type 1 Nuclear Receptor, the VDR (commonly known as the 'Vitamin D Receptor'), is responsible for transcription of LL-37, the human Cathelicidin antimicrobial peptide, as well as the beta-Defensin anti-microbial peptides defB2/defB4 [3]. Disabling transcription by the VDR would allow a pathogen to persist inside phagocytes without threat from these anti-microbial peptides. Static molecular modeling (primarily using AutoDock) was used to screen a number of proteins and peptides known to be produced by the genomes of the gliding bacteria.
RESULTS: A candidate bacterial sulfonolipid, Capnine, was identified to have a nanomolar Ki for the ligand binding pocket (LBP) of the VDR. Molecular Dynamics simulation of the human VDR in complex with Capnine confirmed that this substance is indeed stable in the VDR LBP, and that its action is that of a strong transcriptional antagonist.
CONCLUSION: Medical Metagenomics has demonstrated the ability to deliver important results in-silico, potentially underpinning an infectious pathogenesis for idiopathic chronic illness [4,5].

References:

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