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Drug Discovery Meet 2020- SIRT6 small molecule modulator as a potential anti-inflammatory treatment for targeting TNF-α related disorders

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Abstract:

SIRT6 is a NAD+ dependent deacylase enzyme with a key role in ageing, metabolism and inflammation. Chronic inflammation conditions are often characterized with uncontrolled Tumor Necrosis Factor Alpha (TNF-α), cytokine production. Dysregulation of TNF-α has been implicated in a variety of human diseases including inflammatory bowel disease, Alzheimer's disease, Amyotrophic lateral sclerosis and more. SIRT6 has a dual role in TNF-α inflammatory pathways. SIRT6 can control TNF-α secretion levels by a removal of a myristoyl group from TNF-α K19. Upon deacylation, TNF-α is localized to the cell membrane. If stayed acylated, it is more tended to be degraded by the cell lysosome. After secreted, TNF-α enhancing the inflammatory response in target cells by activating nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB). On the other hand, SIRT6 regulates transcription factor NF-kB by deacetylating Histone 3 K9. Therefore, SIRT6 modulators could become future anti-inflammatory drugs for treating TNF-α related disorders. In order to inhibit TNF-α secretion, we aimed to modulate specifically SIRT6's deacylation activity. We characterized SIRT6 activity and physical interaction with small compounds using a pipeline of in-vitro and in-silico assay systems. As a result, we were able to identify a novel small compound with the ability to modulate TNF-α secretion. Therefore, we suggest this compound as a starting candidate in order to develop new anti-inflammatory drugs.

Biography:

Matan Avivi is currently a Ph.D. student working with Professor Haim Cohen at Bar-Ilan University in Israel. His research focuses on the discovery of small molecule modulators for Sirtuin proteins using in-vitro assay systems and computer aided drug discovery methods. He received a B.Sc. and completed M.Sc. with excellence, both in biophysics in Bar-Ilan University, Israel. In addition to his research, he was chosen to work as an analytical services specialist in the faculty's bioanalytical unit, where he provides services to both industry and academia in the fields of bio interactions and chromatography.

Note : This work is partly presented at 10th international conference on Advanced Drug Discovery and Drug Delivery (London UK, July 15th)