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Inhibition of MST1 kinase activity: Blocking SARAH domain interactions with peptides

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MST kinases (MST1-MST4) are serine/threonine kinases that are involved in different cellular processes including cell polarization, migration and apoptosis. Structurally, MSTs are homodimers composed of a kinase domain, an unstructured regulatory domain and a helical SARAH domain. Their activation is driven by dimerization and trans-auto-phosphorylation. The activity of these proteins is normally highly regulated. Nonetheless, deregulation of their activity associates them with various pathologies, such as cancer and autoimmune disease, making them attractive treatment targets. The MST1 kinase has been identified as a key regulator of apoptotic beta cell death by phosphorylating the pancreatic and duodenal homeobox-1 (PDX1) transcription factor. PDX1 is important for beta cell maturation and pancreatic development. When phosphorylated however, it is ubiquitinated and degraded, which leads to beta-cell apoptosis resulting in impaired insulin secretion and diabetic progression. Therefore, blocking MST1 kinase activation may serve to reduce pancreatic beta cell apoptosis as a rational approach to address diabetes. The most common strategy to inhibit kinases, including MST1, is via small molecules that target the kinase domain active site, which is highly conserved among kinases. In this study, we proposed an alternative approach, the use of peptides to interfere with the SARAH domain interactions which is a key for dimerization and activation of the protein. Indeed, peptides and biologics in general are attracting the attention of the pharmaceutical industry, as this class of drugs that can provide additional scope for novel treatments beyond small molecules. To this end, after conducting a thorough structural study on the MST1 SARAH domains, we have designed three peptides that can possibly block the interactions taking place. These peptides have been tested and the preliminary results show a promising outcome. The same strategy can be employed for other proteins that depend on protein-protein interactions for functional regulation.

Recent Publications:

1. Robertson N and Spring D (2018) Using peptidomimetics and constrained peptides as valuable tools for inhibiting protein– protein interactions. Molecules 23:959.
2. Ardestani A and Maedler K (2016) MST1: a promising therapeutic target to restore functional beta cell mass in diabetes. Diabetologia 59(9):1843–9.
3. Thompson B J and Sahai E (2015) MST kinases in development and disease. Journal of Cell Biology 210:871–82.
4. Fabbro D (2015) 25 years of small molecular weight kinase inhibitors: potentials and limitations. Molecular Pharmacology 87:766–75.
5. Ardestani A, Paroni F, Azizi Z, Kaur S, Khobragade V, Yuan T, et al., (2014) MST1 is a key regulator of beta cell apoptosis and dysfunction in diabetes. Nature Medicine 20:385–97.

Biography

Mahlet Z Tamirat specializes in the areas of structural bioinformatics with an emphasis in computer aided drug design. By employing different bioinformatics techniques, she is able to investigate proteins and explore means to affect their activity by designing small molecules and peptides. These endeavors have shown to be promising, one example being the MST1 kinase inhibition described in this abstract.