Get “Hooked” on

Brugia malayi Asparaginyl tRNA Synthetase

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I. Abstract
A partnership between high school students and a scientist enabled the Brown Deer SMART Team (Students Modeling A Research Topic) to explore the structure and function of asparaginyl-tRNA synthetase (AsnRS), a potential drug target to treat lymphatic filariasis, and to build a 3D physical model of the protein. Lymphatic filariasis results from mosquitoes transferring the nematode, Brugia malayi, to host lymph nodes, leading to swelling of affected limbs. AsnRS hooks asparagine to tRNA, used during protein synthesis. AsnRS is a member of the aminoaeryl tRNA synthetase (AARS) family, a set of structurally heterogeneous enzymes, specific for each amino acid. AARS are potential drug targets as they are essential for survival and are structurally different between species. AARS also functions as an immunosuppressor, blocking interleukin 8 receptors in humans. Current research for treatment targets parasitic AARS. If multiple functions could be mapped to the same region of the protein, a single drug could target these functions. Inhibition of the tRNA-amyinoacylation function of AsnRS would prevent protein synthesis, thus causing death of the parasite. Preventing AsnRS from blocking interleukin 8 receptors, would act as an immunostimulant in humans. Further research on this family of enzymes could provide alternative therapies to treating parasitic diseases.

Over 200 million people worldwide are affected by lymphatic filariasis. The distribution of the disease, as of 2004, is represented by the green colored countries.

II. Disease Aspect
The nematode, Brugia malayi, buries itself in the lymph nodes causing scar tissue to form, inflaming the glands. This restricts the circulation of lymph, making the leg swell to an abnormal size, as seen in the figure below.

B. malayi is dormant during normal daylight hours. The worm can be found in the bloodstream from 10 pm to 2 am causing difficulty in diagnosing the disease. The complex life cycle of the nematode is pictured below:

III. AsnRS Structure and Function

B. malayi asparaginyl tRNA synthetase (AsnRS) functions as an immunosuppressor in humans and is essential for protein synthesis. Asparagine binds to the amino acids (shown in purple in the model above), and ATP binds to the beta sheets (highlighted yellow in the model above).

The main function of AsnRS is to attach asparagine to tRNA by the two step process shown in the diagram above. Disruption of this process interrupts protein synthesis, causing the death of the worm.

IV. Blocking AsnRS Receptors

Research Focus: Identify drugs which will inhibit protein synthesis in B. malayi and be an immunostimulant in humans.

Experimental Objective: Find a chemical that affects chemotaxis by blocking the part of AsnRS important to receptor interaction.

Results:

Conclusion: The experiment demonstrated that 3D6, a monoclonal antibody, subdues the chemotaxis, or movement, towards AsnRS; however, IgG allows AsnRS to continue attracting molecules. Because 3D6 blocks chemotaxis, it was concluded that it does so by blocking the part of AsnRS crucial to receptor interaction.

V. Drug Target

Since the receptor binding site and the tRNA binding site are in close proximity, it might be possible to design a drug to block both. The drug would attach to the hook shown at site (1) in the diagram above, which inhibits protein synthesis in the parasite. Site (2) shown above depicts the region that blocks immunosuppression. Finding a single drug could lead to treatment of lymphatic filariasis.