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Structural Analysis of L-asparaginase from novel source as a Promising Drug Target in the Treatment of Childhood Acute Lymphoplastic Leukemia

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Protein Crystallography is a highly throughput technique used to assess the structure-function relationship of biological macromolecules. Obtaining accurate and reliable three-dimensional structures are the basic pre-requisites for rational drug design. Childhood Acute Lymphoblastic Leukemia (ALL), cancer of white blood is our goal. It comprises the most common kind of childhood cancer. Many underdeveloped lymphocytes are found in a blood and bone marrow; it can spread to other parts of the body including the lymph nodes, liver, spleen and central nervous system (CNS). Among the drugs used in the treatment of ALL are bacterial-derived enzymes called asparaginases that catalyze the conversion of asparagine into aspartic acid and amonia. L-asparaginase has been considered as a unique chemotherapeutic agent against cancer. Leukemic cells and some other suspected tumor cells are unable to synthesize the asparagine, whereas normal cells can synthesize their own asparagine. This deprives the leukemic cell of circulating asparagine, which leads to cell death. The clinical utility of L-asparaginase is often limited by the Asparaginase immunogenicity, developing of drug resistance and toxicity due to repeated dose. Despite the universal inclusion of asparaginase in treatment protocols, there is much debate regarding the optimal formulation and dosage. Therefore, we are planning to investigate the 3D-structure of L-asparaginase from a novel source (chicken liver) as a promising drug target against ALL. Results are expected to provide new insights for: 1) Identifying the structural environment of the substrate binding sites, 2) Enhancing the drug efficacy by immobilization on biocompatible nanoparticles and hence decreasing the aforementioned obstacles that face the therapeutic treatment of ALL, and 3) Increasing the variety of the drug source as there are only two sources (E. coli & Erwinia sp.) available in the market.

Summary

Childhood Acute Lymphoblastic Leukemia (ALL)comprises the most common kind of childhood cancer. It represents about 30% of all pediatric malignancies and 70% of pediatric leukemia. The annual incidence of ALL has been reported by the National Cancer Institute (Egypt) to be four cases per 100,000 children. Among the drugs used in the treatment of ALL, bacterial-derived enzymes known as asparaginases that catalyze the conversion of L-asparagine to aspartic acid and ammonia. L-asparaginase has been considered as a unique chemotherapeutic agent against ALL. Leukemic cells depend on circulating asparagine for protein synthesis process necessary for their survivals. Normal cells have their own machinery for the synthesis of asparagine. The clinical utility of L-asparaginase is often limited by the Asparaginase immunogenicity, developing of drug resistance and toxicity due to repeated dose. Despite the universal inclusion of asparaginase in treatment protocols, there is much debate regarding the optimal formulation and dosage. Therefore, we are aiming to implement X-ray crystallography to perform a structural analysis of asparaginase enzyme from a novel source (chicken liver)to avoid the drug resistance against currently available asparaginases in the market. The results will provide new insight toward the development of drugable targets against ALL.

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