Structural analysis of human lysine specific demethylase 3B used in the context of fragment-based drug discovery

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INTRODUCTION

Polycystic Ovarian Syndrome(PCOS) is a hormonal disorder,associated with chronic oligomenorrhea(Irregular periods), Hirsutism(Unwanted male pattern hair growth) and polycystic ovarian morphology which leads to infertility. Women with PCOS exhibit insulin resistance and compensatory hyperinsulinemia which leads to diabetes. It is also includes physiological impairments with depression and other mood disorders and metabolic derangements. Most of the women with PCOS obese favouring the developement of PCOS phenotype. Reproductive hormones are out of balance. there will be increased levels of androgens(Male hormones) which leads to Hirsutism. Body doesn't react with insulin in case of PCOS, which leads to hyperinsulinemia. Body may not have enough of progesterone. They might miss periods for a long time. Unfortunately there is no cure for PCOS, but it can be controlled by using birth control pills to regularise periods. The drug, metformin is also prescribed to these patients who get diabetic, which is a result of PCOS. The physicians also recommend physical exercise to these patients. WHO estimates that PCOS affected 116 million women(3.4%) worldwide in 2012. In india, 10% women are affected with PCOS and yet no proper published statistical data on prevalence of PCOS is available in India. Socio economic studies from India observed PCOS as a lifestyle disorder, highly prevalent among middle and high income urban population as compared to rural population

The binding protein of PCOS is lysine specific demethylase it is also known as lysine (K)-specific demethylase 3B (KDM3B).It is a protein which regulates the propagation of autophagy via transcriptional activation of autophagy-related genes. KDM3B is a demethylase that specifically removes mono- or dimethylation of histone H3

EXPERIMENTALS

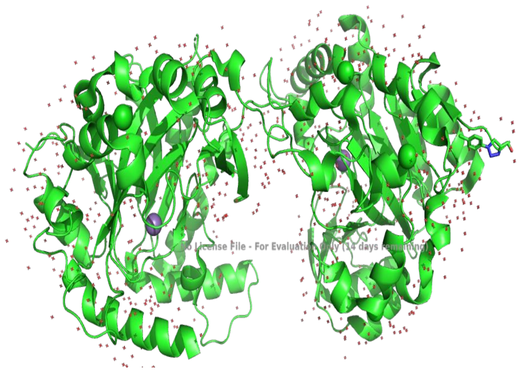
in order to understand the overall structure of lysine specific demethylase 3B protein of Polycystic ovarian syndrome three dimensional analysis of the structure was performed using computational biology tools. Structure of the protein was downloaded from PDB. (PDB id- 5RAA). The analysis include evaluation of secondary structure(alpha helix and beta strands) followed by hydrogen bonding analysis using Pymol software. The R-work value of this protein is 0.1823 i.e, 18.3% and R-free value is 0.210 i.e., 21%

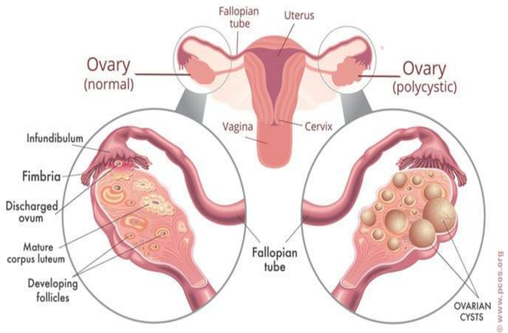
In order to determine the quality of structure we perform two tests i.e.,

1. The R-Work is more than 1/10th of the resolution i.e, 0.157
2. The Difference between R-work and R-Free is 0.027 which is less than 0.05.

So, this is a good structure

3 Small molecules are obtained they are S3Y, MN, CL and 1 macro molecule is obtained. that is lysine specific demethyalse.





Difference between normal and polycystic ovary

RESULTS & DISCUSSION

The structure of PCOS protein contains two chains, which are A-Chain and B-Chain. Both are same so, we consider only one chain. The chain consists of 15 alpha helices and 14 beta strands. 3 small molecules are present in the structure they are S3Y, MN, CL.

There are no hydrogen bonds are present in the structure.

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