Comparative Molecular Dynamics of Aromatase in Ancient and Modern Felines

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Aromatase (P450arom, CYP19A1) is a cytochrome P450 enzyme that plays a crucial role in the rate-limiting step of oestrogen biosynthesis from androgens.[1] It undertakes a three-step oxidative process. Despite the importance of this enzyme, only a few comparative studies have investigated mammalian aromatases for their structural and functional relationship.[2] Hence, this study conducted a computational comparison of aromatases obtained from some cat family species: *Homotherium*, *Felis catus*, *Puma concolor*, *Acinonyx jubatus*, *Panthera tigris* and *Panthera pardus*. The human aromatase X-ray structure was used as a template to create 3D structural models of feline aromatases and classical Molecular Dynamics simulations undertaken in aqueous or membranous environments.

Within the feline family there was high amino acid sequence identity (99%) and also with human aromatase (86%). Comparisons using classical Molecular Dynamics (100 ns) were used to assess the overall stability of aromatases and showed that dimers of feline aromatase were less likely to form based on RMSD/RMSF, surface potentials and hydrogen bonding patterns. Inclusion of a physiological membrane environment to accommodate the transmembrane region of both monomeric and dimeric aromatases provided more stability for these enzymes.

Accelerated molecular dynamics was then used to obtain extended (1 μs) simulations of the human aromatase providing the lowest free energy conformations with the dimeric form in a membrane. The access/egress channels were then probed (with steered molecular dynamics in conjunction with umbrella sampling) using both substrate (androstenedione) and product (oestrone) to define the highest probability pathway. Dimerisation provided a new path for androstenedione to move between the membrane and enzyme via the dimer interface which became more significant for oestrone.

These simulations provide comparative analyses of aromatase structure and function as well as evolutionary significance. Also, complementary data on environmental stressors that influence aromatase activity, needed to understand species reproduction can be gleaned.

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