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LARMD: Integration of bioinformatic resources to profile ligand-driven protein dynamics with a case on the activation of estrogen receptor

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Abstract

Protein dynamics is central to all biological processes, including signal transduction, cellular regulation and biological catalysis. Among them, in-depth exploration of ligand-driven protein dynamics contributes to an optimal understanding of protein function, which is particularly relevant to drug discovery. Hence, a wide range of computational tools have been designed to investigate the important dynamic information in proteins. However, performing and analyzing protein dynamics is still challenging due to the complicated operation steps, giving rise to great difficulty, especially for nonexperts. Moreover, there is a lack of web protocol to provide online facility to investigate and visualize ligand-driven protein dynamics. To this end, in this study, we integrated several bioinformatic tools to develop a protocol, named Ligand and Receptor Molecular Dynamics for profiling ligand-driven protein dynamics. To be specific, estrogen receptor (ER) was used as a case to reveal ERβ-selective mechanism, which plays a vital role in the treatment of inflammatory diseases and many types of cancers in clinical practice.

Two different residues in the pocket of ERβ/ERα were the significant determinants for selectivity, especially Met336 of ERβ. The helix H8, helix H11 and H7-H8 loop influenced the migration of selective agonist (WAY-244). These computational results were consistent with the experimental results. Therefore, LARMD provides a user-friendly online protocol to study the dynamic property of protein and to design new ligand or site-directed mutagenesis. Nuclear hormone receptors (NHRs) are members of a large nuclear receptor family that acts as transcription factors. These are distributed throughout the body and play diverse roles in cellular processes. Nuclear hormone receptors include the androgen receptor, glucocorticoid receptor (GR), progesterone receptor, mineralcorticoid receptor, estrogen receptor (ER)α, and ERβ. The activity of NHRs is modulated by steroid hormones that are derived from cholesterol. Due to their hydrophobic nature, steroid hormones diffuse across the plasma membrane, enabling systemic extracellular signals to regulate tissue specific intracellular events.

Estrogens are one class of steroid hormones that includes estrone, estradiol (E2), and estriol. 17β Estradiol, the most potent estrogen hormone in the circulation, is involved in a wide variety of vital physiological functions that range from the development and maintenance of reproductive organs to the regulation of cardiovascular, musculoskeletal, immune, and central nervous system homeostasis. Estradiol also contributes to the initiation and development of target tissue malignancies. The effects of E2 are mediated by ERα (NR3A1) and ERβ (NR3A2). The dissection of the ER-mediated E2 signaling in estrogen target tissues largely stems from knock out (KO) animal models. Species specific differences in tissue distribution withstanding, it appears that ERα predominates, whereas ERβ plays a minor role, in the uterus, mammary glands, pituitary gland, skeletal muscle, adipose tissue, and bone. Estrogen receptor β, in contrast, is found to be critical in mediating E2 signaling in the ovary, prostate, lung, cardiovascular and central nervous systems. Even within a single tissue, the expression pattern of each subtype is cell type specific.

In the ovary, for example, ERβ is expressed in the granulosa cells but ERα is more abundant in the theca cells. Reflecting the different ER subtype distribution patterns, ERαKO and ERβKO mice show different phenotypes. The ERαKO female mice are, for example, infertile with a hypotrophic uterus, as well as with anovulatory and hemorrhagic ovaries. In contrast, the ERβKO female mice are subfertile and display reduced ovulation, probably as a result of a retardation in granulosa cell differentiation.

Although significant progress has been made towards understanding the mechanism of ERβ signaling since its discovery in 1996, many aspects of ERβ's actions and its role in the physiology and pathophysiology of E2 signaling remain unknown. This is due to, as indicated by one study, at least in part, because of the lack of established experimental cell models that synthesize ERβ endogenously and of receptor specific antibodies. Nevertheless, accumulating evidence from in vitro, in cellula, and in vivo systems has broadened the understanding of both ER subtype actions in E2 signaling. This communication aims to summarize a current state of understanding of E2–ER signaling by pointing out the similarities, as well as the differences, between the receptor subtypes.