Institutionen för biovetenskaper och näringslära

ER Subtype-Specific Regulation of Estrogen Signaling

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ABSTRACT

The estrogen receptor (ER) isoforms, ERα and ERβ, mediate the physiological functions of the female hormone estrogen. They share high degree of similarity but also show significant differences in many aspects, such as cell and tissue distribution. The activities of ER are tightly regulated by different factors at multiple levels. The biological action of estrogen is the result of a balance between ERα and ERβ activities; and disruption of this balance leads to various health disorders. Understanding the mechanisms of ER subtype specific regulation is critical to understand estrogen signaling in health and disease. In this thesis, we study the possible mechanisms by which estrogen signaling could be regulated in an ER subtype-specific manner.

Intracellular ERα and ERβ protein levels or ERα/ERβ ratio are important determinants for estrogen action. Cellular regulatory factors could affect estrogen signaling by direct regulation of intracellular levels of individual ER isoforms. In ***paper I*** we demonstrate that the circadian system specifically modulates the expression of ERβ. We show that circadian regulators are recruited to the E-box enhancer in ERβ promoter and regulate the transcription of ERβ. Thus, the intracellular level of ERβ as well as ERα/ERβ ratio vary significantly at different times of the day.

Cellular factors could affect the transcription also by regulating ERs on the estrogen target gene promoter. In ***paper II***, we show that the hepatitis B virus X protein associated protein 2 (XAP2) also known as ARA9 influences estrogen signaling by interacting with ERα on the promoter region of ER-target gene in breast cancer cells. Through this mechanism, XAP2 regulates the estrogen target gene transcription in an ER subtype-specific manner, as XAP2 inhibits ERα, but not ERβ-mediated transcription.

In ***paper III*** we identify a novel epigenetic mechanism under the ER subtype-specific regulation of gene expression. We show that ERβ, but not ERα, is essential in maintaining the unmethylated state of one specific CpG in glucose transporter 4 (Glut4) promoter. This CpG is part of a specificity protein 1 (Sp1) binding site and this regulation is important for normal Sp1 recruitment and Glut4 transcription in adipocytes.

In conclusion, we have identified three novel pathways in mediating the ER subtype specific regulatory effects.

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