Critical Illness-Related Corticosteroid Insufficiency (CIRCI)

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Figure 2. Glucocorticoid Synthesis and Signaling

Glucocorticoids (e.g., cortisol) are synthesized from cholesterol in the mitochondria by two P450-type enzymes, CYP11B1 and CYPB11B2 and may exert genomic and non-genomic effects. Glucocorticoids diffuse through cell membranes and bind with glucocorticoid receptors (GR, classic GR and MR, mineralocorticoid receptor). Glucocorticoid receptors reside in the cytoplasm in a multiprotein complex with chaperone proteins, heat shock proteins and immunophilins. The classic GR (specifically GR-α) is the major receptor involved in mediating the glucocorticoid responses to stress and inflammation. Upon binding of cortisol, the GR undergoes a conformational change that allows it to dissociate from the chaperone proteins and translocate into the nucleus and the mitochondria where it binds to glucocorticoid response elements (GRE) to activate (transactivation) or repress (cis-repression) pro-inflammatory gene expression of various transcription factors (TFs) such as nuclear factor-kappa B (NF-KB) and activator protein-1 (AP-1).