Speculations on the role of the microtubule network in glucocorticoid receptor signaling

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Abstract

The glucocorticoid receptor (GR) is an important player in the life of a cell. This is underlined by a cohort of protein and nucleic acid structures interacting with the GR. Among many issues surrounding GR activity that are under active investigation, the role of microtubules (MTs) is still unclear. This article aims to evaluate the ayes and noes in favor of microtubule importance and then form a hypothesis on their function in GR activity.

Abbreviations: AP-1, activator protein 1; ARC, activator-recruited cofactor; ASK, apoptosis signal-regulating kinase; CAR, constitutive androstane receptor; CDK, cyclin dependent kinase; C/EBPβ, CCAAT-enhancer-binding protein beta; CBP, CREB binding protein; CIP, CBP-interacting protein; COL, colchicine; COX-2, cyclooxygenase 2; CREB, cAMP-response element binding protein; DEX, dexamethasone; DOC, docotexel; DRIP, vitamin D3 receptor-interacting protein; ERK, extracellular signal-regulated kinase; GC, glucocorticoid; GR, glucocorticoid receptor; GRE, glucocorticoid responsive element; hGR, human glucocorticoid receptor; hsp70 (90), heat shock protein 70 (90) kD; GRIP, glutamate receptor interacting protein; IL-1Rα, interleukin 1 receptor alpha; IL-2R, interleukin 2 receptor; IL-6, interleukin 6; IxB-α, inhibitor kappa B alpha; JNK, c-Jun N-terminal kinase; JNKK, JNK kinase; MAPK, mitogen activated protein kinase; MEKK1, MAPK kinase kinase; MIA, microtubule interfering agent; MTs, microtubules; NFκB, nuclear factor kappa beta; NOC, nocodazole; p23 (p50, p59, p65, p130, p300), protein 23 (50, 59, 65, 130, 300) kD; PAC, paclitaxel; PKA, protein kinase A; PXR, pregnane X receptor; RAC, receptor-associated coactivator; rGR, rat glucocorticoid receptor; SAPK, stress-activated protein kinase; SEK1, SAPK or ERK kinase; SRC-1, steroid receptors coactivator 1; STAT, signal transducer and activator of transcription; TFs, transcription factors; TIF, transcriptional intermediary factor; TNFα, tumor necrosis factor alpha; TRAM, thyroid hormone receptor activator molecule; TRAP, telomerase regulation-associated protein; VIN, vincristine

Introduction

The glucocorticoid receptor (GR) is a member of the steroid/thyroid receptor family. It plays a pivotal role in maintenance of cell homeostasis, growth and development, cell differentiation and proliferation, host defense, inflammation combat, and many other essential
cellular functions. Thus, it is a crucial factor for cell survival and function. A vast number of papers on GR are published annually dealing with receptor function, properties, regulation, interactions, relations to a variety of other processes, etc. The main goal of the majority of studies published has been to unveil the role of the GR in asthma pathogenesis, a disease devastating a considerable portion of populations in developed countries. Studies on the GR are varied, hence many review articles summarizing the current knowledge on particular aspects of GR function are written annually. This paper endeavors to bring new insight into the role of the microtubule network in GR signaling, an important phenomenon in general. The observations in the literature are somewhat ambiguous regarding the necessity and importance of microtubules (MTs) in proper GR functioning. The information discussed in this review comprises both published data and our own experience and observations.

Glucocorticoid receptor structure and function

An important member of the steroid-thyroid receptor family, GR takes part in differentiation, the regulation of metabolic processes, and in combat against inflammation (Schaaf and Cidlowski, 2002; Yamamoto, 1985). It is expressed in virtually all tissues, possessing the capacity to regulate gene expression in a cell type-specific manner. Two forms of human GR, transcriptionally active GR-α and the inactive GR-β, differ at their carboxy termini and have molecular masses of 95 and 90 kDa, respectively (Hollenberg et al., 1985). More recent data suggest the existence of an alternative translation of human GR resulting in synthesis of GR-α and GR-β with molecular weights of 94 and 91 kDa, respectively (Yudt and Cidlowski, 2001). GR protein contains a ligand binding domain, a DNA binding domain consisting of two zinc-fingers, and two transactivation domains (Beato et al., 1995). Full transactivation of target genes requires the presence of both activation domains in hGRz, AF1 and AF2 (Hollenberg and Evans, 1988). The transcriptional activity of the GR depends additionally on co-activators that facilitate recruitment of the basal transcription machinery or remodel chromatin. The homologous coactivators CBP and p300 interact directly with AF1 and indirectly with AF2 of the hGRz, and both possess histone acetyltransferase activity (Chakravarti et al., 1996). The interaction of CBP/p300 with AF2 is mediated by SRC1/NCoA-1 coactivator (Yao et al., 1996), a member of the p160 family of coactivators, containing GRIP1/ TIF2/NcoA-2 (Hong et al., 1997) and AC3/ACTR/NcoA3/TRAM1/p/CIP. Their main interaction site is AF2, and this interaction is mediated by ‘LXXLL’ motifs in NR boxes in the coactivator protein. GR interacts with the DRIP complex of proteins, which is related to the TRAP and ARC complexes (Ito et al., 1999; Rachez et al., 1999). These complexes are known to interact with and coactivate several nuclear receptors.

In the absence of a ligand, i.e. glucocorticoid (GC), GR is predominantly localized in the cytosol in complex with chaperone proteins hsp90, hsp70, and hsp90-binding immunophilins. The complex of GR and its chaperones moves along intact microtubules from the cytosol to the nucleus (Pratt et al., 2004). Regardless of whether a GC is present or not a dynamic equilibrium exists between the cytosolic and nuclear hGR (Nishi et al., 1999). This equilibrium is clearly affected by nuclear import of GR mediated by at least two amino acid sequences (Savory et al., 1999), as well as nuclear export facilitated by DNA-binding domain of GR (Black et al., 2001) and mediated by calreticulin (Holaska et al., 2001). Upon GC binding, GR translocates to the nucleus where it forms a homodimer that binds