Hypothesis

Receptor Accessory Proteins and Glucocorticoid Receptor Activation

A Novel Model in Inflammatory Response

Xiaofeng Shen, MD, MPH; Wei Wang, MD, MSc; Yusheng Liu, MD, MSc; Liming Lei, MD, MSc; Haibo Wu, MNr; Shiqin Xu, MD, MPH; Shan-Wu Feng, MD, PhD; Fuzhou Wang, MD, PhD

SUMMARY

Inflammation is the initial step of physiological defense against injury, and also the mainstay of the pathogenesis and development of different diseases. The balance between pro- and anti-inflammation is maintained through the involvement of various molecules. The activation of glucocorticoid receptor (GR) plays an essential role in contributing to the anti-inflammatory effect of endogenous cortical steroids and exogenous glucocorticoids (GC). During the GR activation process, receptor accessory proteins (RAPs) are important parts functioning as critical components of GR-associated signaling cascades. The binding of GR with its ligand GC and the subsequent transfer of heterologous receptor complex need the participation and regulation of various molecular chaperones. Determining the precise interaction between GR and the RAPs can help to understand the underlying molecular mechanisms of GR activation, and to insight into the potential therapeutics of GC-related treatment. We herein review the up-to-date development of RAPs, and present a new model of GR signaling activation.■

KEYWORDS Glucocorticoid receptor; Immunoaffinity protein; FK506; Molecular chaperone; BAG-1; Heat shock protein

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Author Affiliations: Author affiliations are listed at the end of this article.

Equal Contributors: Shen, Wang, and Liu

Correspondence to: Dr. Fuzhou Wang, MD, PhD, Department of Anesthesiology, Nanjing Maternity and Child Health Care Hospital, Nanjing Medical University, Nanjing 210004, China
Email: zfwang50@njmu.edu.cn

As one of the ligand-dependent transcription factor family members, the glucocorticoid receptor (GR), usually freely shuttles between the cytoplasm and the nucleus in either hormone-free or hormone-binding states. The balance of the movement of GR between cytoplasm and nucleus determines if GR is in a dominant status in cytoplasm or nucleus, which affects a variety of physiological functions of cells (1). The transfer and functioning of GR depends on the involvement of a variety of accessory proteins in cytoplasm, i.e., receptor accessory proteins, including immune affinity protein (FKBP51, FKBP52), molecular chaperone BAG-1, and heat shock proteins (HSPs) (2-4). The receptor-mediated signal transduction and the maintenance of the regulatory balance are mainly through receptor accessory protein. This review paper mainly focused on the roles of RAP, the new model of its interactions with GR, and the related diseases and treatments.

INTERACTIONS BETWEEN RECEPTOR ACCESSORY PROTEIN (RAPS) AND GR

Immunoaffinity Protein (Immunophilin)

Immunoaffinity protein was originally named because of its high affinity with the immunosuppressant FK506 and cyclosporin A. Its NH2 terminal motif has the peptidyl prolyl isomerase (PPIases) activity, which can convert the prolyl peptide of target protein from cis isomer into trans isomer. Its COOH-terminal motif contains three thirty-four-peptide repeat sequences, which degrades 34 repeated amino acid sequences during the protein-protein interactions (5).

FKBP51 and FKBP52 have different biochemical functions while both of them belong to FK506 immunophilin binding to protein with large molecular weight. They play an important role in the formation of steroid hormone-receptor complex, and mediate three different major physiological processes in cell, i.e., nuclear receptors assistance, the open of calcium release channel, and the receptor protein kinase activation (6). The multiple interval peptidyl prolyl cis-trans isomerase activity which is involved in the formation of the nuclear receptor heterologous complex widely exists, and keeps the receptor protein in the functional folded state in the presence of HSP90. In mammals, FKBP51 and FKBP52 regulate GR mainly through two different mechanisms: the hormone binding and GR nuclear transfer (7).

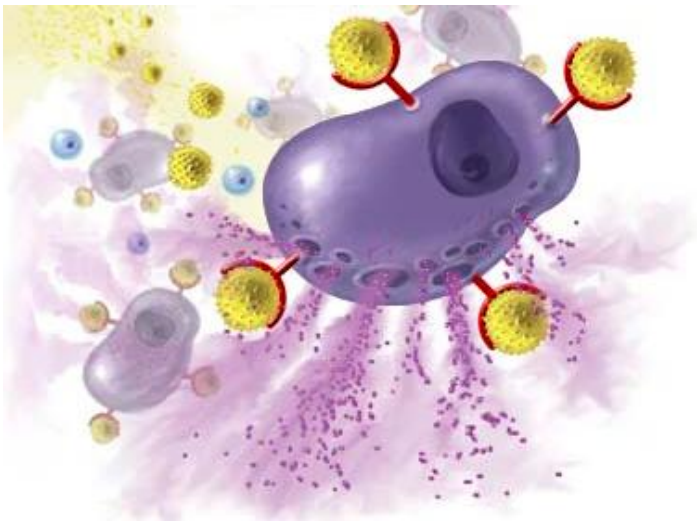
In primates, progesterone-induced the increase of FKBP51 expression may impair the reactivity to progesterone, significantly decrease the binding of GC to GR and the activity of GR. FKBP51 overexpression may be one of the reasons of the decreased binding capacity of the progesterone receptor (PR) complex which leads to the progesterone resistance (8). Moreover, an immunosuppressant FK506 and rapamycin are also involved in GC resistance by acting on FKBP51 to change the binding of GC and GR. However, FKBP51 remains one of the routine members of free high-affinity GR complex. GR signal transduction is regulated by the same way of the regulation of FKBP51 to PR. The overexpression of FKBP51 in monkey is one of the reasons leading to progesterone resistance. However, it is not clear yet this mechanism is also involved in the resistance to other steroids.

FKBP52 plays an important role in the steroid receptor functioning, and participates in a variety of other physiological processes including the regulation of growth and development, transcriptional regulation, regulation of the cation channel activity, regulation of the efficiency of gene conversion, neuroprotection and the regulation of the myocardial nutritional role of nutrients 1 (2, 9). FKBP52 regulates the capacity of GR receptor binding and strengthens GR-dependent transcriptional activity through its characteristics of PPIases. However, PPIases-deficient FKBP52 can still interact with dynein, while it strongly inhibits GR-dependent transcription (10). In addition, the effective regulation of FKBP52 on GR signaling is dependent on its reaction with HSP90 and its binding to dynein: on the one hand, the phosphorylation of Thr143 by casein kinase II controls the binding of FKBP52 to HSP90, competitively with other TPR protein binds to TPR region so that it interacts with HSP90 and belongs to the GR heterologous complex; on the other hand, FKBP52 is closely related to the GC-activated receptor movement, regulates signal transduction via binding to PPIases region, and transfers GR to the nucleus along the cytoskeleton through its reaction with microtubule-dynein (11).

BAG Family Molecular Chaperone Regulator 1 (BAG-1)

As a molecular chaperone of nuclear receptor protein, BAG-1 interacts with retinoic acid receptor (RAR) and

causes the inhibition of the binding of RAR to DNA response element binding, and RAR-dependent transcription (12). Moreover, the transcriptional activity of GR was also significantly affected. BAG-1 plays critical roles in a variety of important physiological and pathological processes including the regulation of apoptosis, oncogenesis, neuronal differentiation and the reactions of cellular regulatory proteins including GR. BAG-1 binds to GR hinge region and inhibits DNA binding and the transcriptional activity of the GR receptor, and, therefore, plays a role in the negative regulation of GR (13).



BAG-1 competes with the stimulating activity of HSP70-interacting protein (HIP), while, in turn, HIP antagonizes the negative regulatory role of BAG-1 on GR's binding to GC. The inhibitory effect of BAG-1 on GR-dependent transcription is related to its reaction region of HSP70. The binding site of BAG-1 to HSP70 is in the same molecule of its DNA binding sites (14). BAG-1 not only affects the folding and related transcriptional activity of GR, but also directly but non-specifically binds to DNA and activates non-GR-dependent transcription of target genes. This activity can disappear by the deletion of 10 amino acids at its N-terminal. In addition, BAG-1 can transfer into the nucleus through its HSP70 binding region at C-terminal, and then functions in combination with GC or GR (15).

Heat Shock Proteins (HSPs)

HSP is a superfamily of proteins which is widely present in the cells and participates in a variety of physiological and pathological processes. It not only plays important roles in the maintenance of the necessary protein conformation and protects cellular activities under stress conditions, but also promotes protein molecule folding, transmembrane transport, displacement and cytoskeleton stability and other basic physiological functions (16). It is also involved in the immune regulation, apoptosis, heat intolerance, and anti-virus and anti-tumor activities. HSP 70 and HSP90 are the two main molecules in HSP family that play a major role during GR functioning.

HSP70 is involved in the protein transferring into endoplasmic reticulum through its functions on protein folding, which facilitates the maintenance of enzyme kinetics and cell function. It has been clear that the role of molecular chaperone of HSP70 depends on the cycling reaction of intracellular ATP (17). The conversion process between ATP and ADP is associated with the process of combination and separation of HSP70 with a polypeptide. The supporting roles of HSP70 to GR are mainly through the following mechanisms: BAG-1 that comes from the same gene but with different starting translation sites can inhibit HSP70-dependent activity of protein refolding; HSP40 can increase the in vitro HSP70 ATPase activity and HSP70-dependent refolding which leads to the GR stabilization; different from the characteristic of the positive regulatory factors of HIP's HSP70 chaperone activity, C-terminal of HIP inhibits HSP70 ATPase activity and impairs the stability of HSP70's substrate complex (15, 18).

The changes of HSP90 protein expression and the mutations of HSP90 gene are closely related to the decreased GC reactivity and effectiveness. The interaction between HSP90 and PPIases region of FKBP52 and the receptor protein GR enables it in the condition of functional folding, and thus plays an important regulatory role in the functions of GR (19). As the HSP90 molecular chaperone inhibitors, Geldanamycin and its low-toxic derivative 17-AAG, through their competitive binding to HSP90 with ATP/ADP, can cause the degradation of a variety of signaling proteins including steroid hormone receptors (20). This is critical for better understanding the mechanisms by which GR mediates the regulation of HSP90 on cell functions.

RECEPTOR ACCESSORY PROTEIN AND THE NEW MODEL OF GR ACTIVATION

GR is a single chain phosphoprotein composed of 800aa. Its structure mainly consists of several separate and in-

dependent functional regions: (i) DNA binding domain (DBD): in charge of the binding with GC response element (GRE) on the promoters or enhancers of target gene; (ii) The hormone binding domain (HBD) at COOH terminus: in addition to the binding to hormone ligand, being involved in the formation of GR dimers and binding to HSPs; (iii) Immunogenic region (ID) at NH2 terminus: having a specific antigen activity and participating in GR's transcriptional transactivation on target genes; (iv) Taul region near HBD: being mainly involved in the nuclear translocation of GR.

Without the presence of ligand, GR locates in cytoplasm and binds to a 300KDa protein complex which is formed by several chaperone molecules and competes with hormone binding. The key step of this process is the binding of HSP90, HSP70, Hsp70/Hsp90 organizing protein (HOP) and HIP, and HSP90 to the COOH terminus of GR, their participating in GR's folding configuration and preventing its translocation from the cytoplasm to the nucleus, forming the initial complex of these four factors with GR in the present of HSP40; Then HSP70 and HIP may separate from HOP, causing p23 and FKBP51 entering and ATP-dependent formation of the terminal complex, which gives GR the competitiveness for GC binding; While the terminal complex with the competitiveness of GC binding recruits dynein, it binds to the GC ligand in cytoplasm and induces the exchange of FKBP52 and FKBP51. FKBP51 is replaced by FKBP52, and ultimately enters into the nucleus in the form of activated complex of GR 2HSP90/P23/HSP40/FKBP52/Dynein/GR/GC. After entering into the nuclear, the steroid receptor accessory protein separates from GC/GR and the active GR can identify the sequence of glucocorticoid response element (GRE). Since GRE locates in the promoter region of the target gene of GC, it can induce or suppress the expression of target genes and, therefore, has physiological and pathological effects.

The study found HSP70 and HSP90 play the roles not only in the cytoplasm: HSP70 plays a supporting role during the process of activated GR and BAG-1 entering into the nuclear. HSP90 is involved in the subcellular substrate transfer and the chromatin recycling of GR. Moreover, the reactive molecule of HSP90, p23, participates in chromatin assembly and the regulation of GR activation. Like p23 is dependent on HSP90, BAG-1 is dependent on HSP70 to play a role in the dissociation of the transcription complex in the nucleus. In this model of GR signaling transduction, the direct reaction of FKBP52 with HSP90, and the exchange between FKBP51 and FKBP52 are critical for GR activation and complex transfer. FKBP52 is indispensable for the nuclear translocation of GR, while FKBP51 induces GR out of the nuclear and participates, together with HSP90, in the GR recycling.

RECEPTOR ACCESSORY PROTEIN AND GR-RELATED DISEASES AND TREATMENT

Given the important roles of immune cells in the development of systemic inflammatory response syndrome (SIRS), it is particularly important of the HSPs expression in monocytes/macrophages and neutrophils for the pathogenesis, development and prognosis of SIRS (21). HSPs regulate the expression of proinflammatory mediators by inhibiting the nuclear translocation of NF-κB and by inducing I-κB gene expression, and thus indirectly reduce the expression of proinflammatory cytokine. Furthermore, overexpression of HSP70 in cells can reduce the H_2O_2-mediated protein oxidation, lipid peroxidation, and thus plays a cytoprotective role (22). HSPs protect from pathological damage of SIRS through the mechanisms of anti-apoptosis, anti-inflammatory and molecular chaperone.

FKBPs, BAG-1 and HSPs involved in the GR signaling transduction might be closely associated with many GR dysfunction-related diseases. First, the GR mutation or the limitation of HSP90's function leads to the abnormality of GR functions. Second, either inhibitory co-molecular chaperone BAG-1 or agonistic molecular chaperone FKBP5 is the important reason of GC resistance (23). Recent studies have found that in steroid-resistant primary nephrotic syndrome (NS), in addition to the changes of total GR level in the body, the more important reason for GC resistance might be the imbalance of the two isoforms, GRα and GRβ, with GRβ expression upregulated and GRα expression downregulated, while the total GR level is unchanged (24).

The GR-mediated inactivation of MAPK benefits cell survival, even if the cell apoptosis reduces and tumor expands. HSPs play an important role in cell growth and apoptosis through its participating in the Fas death receptor pathway, caspase pathway and JNK/SAPK pathway. HSP70 inhibits cell apoptosis through its binding to stress-activated protein kinase (JNK) and inhibiting its activity, as well as the same mechanisms of anti-apoptosis of Bcl-2 family mainly

including inhibiting the activation and the precursor processing of caspase 3 and caspase 9 at the upstream and downstream of caspase activation, respectively; The antiapoptotic multifunctional protein, BAG-1, is the nucleotide conversion factor of the heat shock cognate protein 70 (HSC70) and its ATP-ADP cycling. Its anti-apoptotic function is through its regulation on the chaperone activity of HSP70 (25). Thus, through the regulation of MAPK and the related transduction pathways, GR and HSPs have different regulatory roles in different disease. It inhibits or promotes ERK and JNK phosphorylation, and, in turn, reduces or increases ELK phosphorylation and many ELK1-dependent target gene expressions, and therefore, has therapeutic effects.

GC upregulates the gene transcription of FKBP51 in leukemia cells. These genes are located at the upstream of the GC-induced apoptosis protein family Bcl-2. Even in the presence of protein synthesis inhibitor cycloheximide, GC is able to upregulate this gene, indicating that FKBP5 directly induces GR's target genes. The intron 2 of FKBP5 has a GC response element and mediates the GC reactivity. The upper and lower component of this response element is surrounded by a full (A/T) G (A/T) (A/T) C (A/T) sequence and 2 incomplete (A/T) G (A/T) (A/T) C (A/T) sequences from 2-4 split nucleotides. Thus, the regulation of GC target gene expression may improve the effectiveness of treatment in leukemia and lymphoma patients (26).

The polymorphism and the fast response to stress of FKBP5 are closely related to its rapid response to the treatment of anti-stress. It is, therefore, associated with the adaptive changes of cytoplasmic GR's function, which not only quickly restores the functions of impaired hypothalamus-pituitary-adrenal (HPA) axis, but also causes the overreaction of GC during the stress (27). An appropriate adjustment and regulation of FKBP5 that improves GR function and makes HPA axis to play more beneficial role might be an ideal therapy for the stress disorders. Preconditioning of FK506 may reduce the endotoxin-induced acute liver injury by decreasing serum TNF-α and IL-1β content, reducing the inflammation, and thus exerting the anti-inflammatory effects (28).

A study using a transgenic mouse model with heart failure that overexpresses FKBP apoptotic sequence protein showed the mutated FKBP apoptotic sequence protein induced spontaneous cardiac pathological death, while the inhibition of apoptosis of cardiomyocytes in this heart failure model improved myocardial function (29). These results suggest that the activation of FKBP apoptotic sequence protein and the apoptosis of cardiomyocytes is one of the causal mechanisms of heart failure. The inhibition of this process might become a fundamental and new treatment strategy for heart failure patients. Rapamycin (RPM) is a 31-membered ring triene macrolide lactam, whose structure is similar to FK506 but with high Lipophilicity. RPM blocks signaling transduction through different cytokine receptors, and blocks cell cycle from G1 to S phase in T lymphocytes and other cells, so that it has the effects of immune suppression and anti-cell proliferation. RPM is an immunosuppressant that is more effective than FK506 or cyclosporin A (CSA), while its side effects are significantly less than FK506 or CSA. In vitro study shows it inhibits human and rat aortic smooth muscle cell division and migration by inhibiting cell division cycle kinases and retinoblastoma protein phosphorylation (30). These effects can prevent the occurrence of the restenosis after percutaneous transluminal coronary angioplasty and the acute artery disease after cardiac transplantation.

The ligand of immunoaffinity protein, FK506, is a macrolide antibiotic extracted from the soil fungus. Its molecular formula is C44H69NO12·H2O and molecular weight is 822.05Da. It has the characteristic of neurotrophic drugs. Recent studies have found that FK506 receptor - immunoaffinity protein is abundant protein in the brain. Its expression dramatically increases especially during the nerve injury (31). Both in vivo and in vitro studies have shown that FK506 and its synthetic mimics promote axonal growth and have neuroprotective effect in a variety of neurons (including DA neurons) (32). Thus, the drug designed to target on the structure-activity relationship of immunoaffinity protein has become a hot topic in drug research for the treatment of Parkinson disease (PD).

The main cells that tacrolimus (FK506) targets on are T lymphocytes. It closely binds to specific cytosolic protein, i.e., immunoaffinity protein, or FKBPs, and inhibits the expression of early lymphocyte-related genes. Furthermore, it also inhibits IgE-mediated histamine release from skin mast cells, which is suitable for the treatment of moderate to severe atopic dermatitis (33).

The study using immunohistochemical analysis of tissue microarrays on the expression of BAG-1 in breast cancer, colorectal cancer, adjacent tissues and normal tissues has shown that the expression of BAG-1 in breast cancer and colorectal cancer is higher than that in paraneoplastic and normal tissue. The high expression of

BAG-1 in breast cancer and colorectal cancer indicates that BAG-1 may be involved in the regulation of cell apoptosis and differentiation in breast cancer and colorectal cancer (34). These finding may provide a more direct intervention method for the diagnosis and treatment of breast cancer and colorectal cancer.

THE PROBLEMS NEED TO BE ADDRESSED

(i) Receptor accessory protein is involved in the regulation of GR functions. It needs further study to investigate whether the pro-inflammatory cytokine-macrophage migration inhibitory factor (MIF) is associated with the receptor accessory protein when GC resistance occurs in a variety of diseases including inflammatory diseases.

(ii) The production of intracellular NO increases in septic shock, while NO, in turn, affects the effective functions of GC. Therefore, more studies are needed to determine if there is a complex interrelationship of mutual regulations among NO, iNOS, receptor accessory protein, MIF, GR, GC and other pro/anti-inflammatory factors.

(iii) The secretion of GC is regulated by ACTH, while Ca^{2+} is needed when ACTH acts on GC. Ca^{2+} plays an important role during the activation of GR by GC. It is still unclear the relationships among Ca^{2+}, receptor accessory protein, GR and GC.

(iv) In addition to immunosuppression, FK506 also has the neurotrophic effects. Further studies confirmed that these two effects were independent of each other, suggesting that it is possible to only use the neurotrophic activity of FK506 to promote nerve growth without affecting the body's immune function. It is worth to explore how to use the immunosuppression effects of immunosuppressant and the neurotrophic effects of FK506 in the clinical peripheral nerve repair, inhibiting the autoimmune response after nerve injury, promoting nerve repair, regeneration and functional recovery.

(v) The antioxidant roles of HSPs may be mediated by the following mechanisms: i) the depletion of the oxidant heme protein; ii) producing the anti-oxidants - biliverdin and bilirubin; iii) increasing the intracellular levels of free iron and the expression of iron related proteins; vi) increasing the basic level of intracellular cGMP.

(vi) Further studies are needed to clarify: during the developmental process of SIRS, the relationship between the levels of cytokines and inflammatory mediators and the HSP70 expression in immune cells, and the effects of the ability and levels of HSP70 expression on the prognosis; to seek the ideal HSPs-inducing drugs and the better strategy for gene therapy. The intervention on HSPs expression in different cells might be a new strategy for the prevention and treatment of SIRS and other critical diseases.■

ARTICLE INFORMATION

Author Affiliations: Department of Anesthesiology, Nanjing Maternity and Child Health Care Hospital, Nanjing Medical University, Nanjing 210004, China (Shen, Wang, Liu, Lei, Wu, Xu, Feng, Wang).

Author Contributions: Dr. Fuzhou Wang had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
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