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Review

Molecular pathways involved in the transport of nuclear receptors from the nucleus to cytoplasm

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ABSTRACT

Nuclear receptors (NRs) are transcription regulators that direct the expression of many genes linked to cellular processes, such as proliferation, differentiation, and apoptosis. Additionally, some cellular events are also modulated by signaling pathways induced by NRs outside of the nucleus. Hence, the subcellular transport of NRs is dynamic and is modulated by several signals, protein–protein interactions, and posttranslational modifications. Particularly, the exit of NRs from the nucleus to cytoplasm and/or other compartments is transcendental, as it is this export event, which determines their abundance in the cells' compartments, the activation or attenuation of nuclear or extranuclear pathways, and the magnitude and duration of their effects inside or outside of the nucleus. Consequently, an adequate control of the distribution of NRs is critical for homeostasis, because a deregulation in the nucleo-cytoplasmic transport of NRs could be involved in diseases including cancer as well as metabolic and vascular alterations. In this review, we investigated the pathways and molecular and biological aspects that have been described for the nuclear export of NRs so far and their functional relevance in some diseases. This information suggests that the transport of NRs out of the nucleus is a key mechanism for the identification of new therapeutic targets for alterations associated with the deregulation of the function of NRs.

1. Introduction

Nuclear receptors (NRs) are a superfamily of proteins expressed in all animals, from the simplest organisms, such as sponges, to the more complex ones, such as mammals. Humans have been identified to have 48 genes that encode different NRs, which are expressed in a tissue and cell context-dependent manner. Their structure comprises of several conserved domains that include an activation function domain (AF-1), a DNA-binding domain (DBD), a ligand-binding domain (LBD), and the activation function domain 2 (AF-2) (Fig. 1A). The LBD recognizes specific ligands that are lipophilic molecules, such as steroid hormones, thyroid hormones, fatty acids, and synthetic products, such as tamoxifen and thiazolidinediones; however, the ligands are unknown for some NRs that are denominated orphan NRs [1–3].

The NRs can be distributed in the cytoplasm and nucleus or can be membrane-associated according to the type of NR and its cellular context. In general, NRs have a genomic signaling pathway, which is initiated by the ligand's binding to LBD. This binding induces conformational changes in the NR that promote its accumulation inside the nucleus and its transcriptional activity. In this compartment, the DBD allows the interaction between NR and specific palindromic sequences localized in the regulatory DNA regions, such as enhancers and promoters. Furthermore, AF-1 and AF-2 promote the association with transcriptional coregulators to activate (coactivators) or repress (corepressor) gene expression. The AF-1 recruits coregulators in a ligand-independent manner, whereas AF-2 requires ligand binding for the interaction with coregulators. Additionally, inside the nucleus, some NRs can also act as coregulators. For instance, the estrogen receptor alpha (ERα) has the ability to function as a coregulator for transcription factors as AP1, Sp1, NF-kappaB, in order to modulate gene transcription [4–9]. Thus, the activity as regulators of gene expression is the classical function of NRs.

Furthermore, some NRs have a non-genomic signaling pathway, since they are localized in the plasma membrane following a post-translational modification, such as palmitoylation, or because of their association with transmembrane receptors. They can also be present in the cytoplasm, where they interact with different proteins to mediate several signaling cascades involving the activation of kinases and the participation of different second messengers. As a consequence, the activation of NRs can also produce rapid cellular responses [4,8,9].

Estrogen receptors (ERα and β), and androgen receptor (AR) are some examples of NRs with critical extranuclear functions. The

Abbreviations: NRs, nuclear recepors; LBD, ligand-binding domain; DBD, DNA-binding domain; CRM-1, chromosome region maintenance 1; CRT, calreticulin; NES, nuclear export sequence; BC, breast cancer; PC, prostate cancer; LMB, leptomycin B

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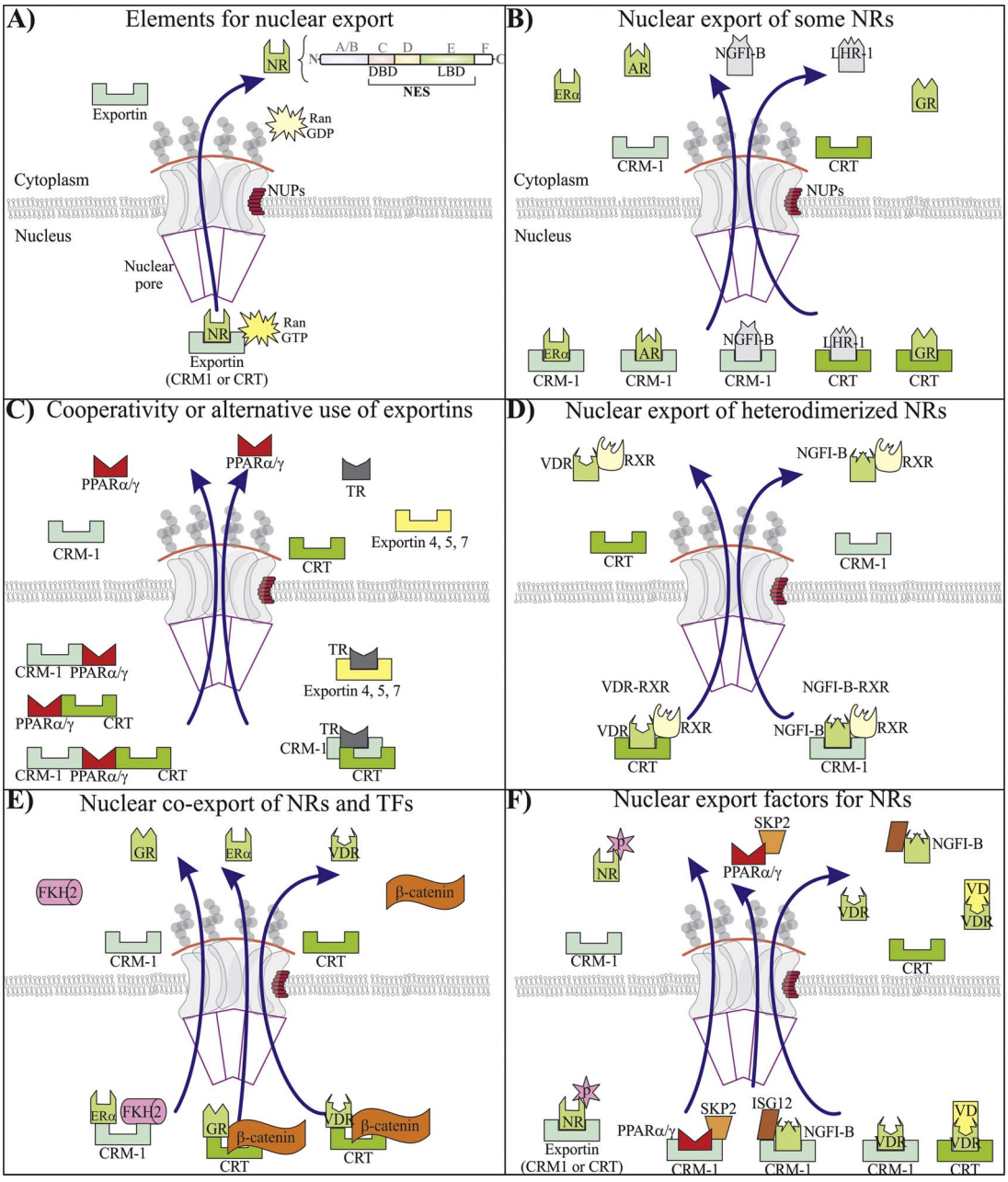

Fig 1. Mechanisms for the nuclear export of NRs in several cellular contexts.

extranuclear activity of ERα is the most studied; several reports indicate that the transcriptional activity of ERα may not be required for many of the functions of this receptor. ERα is palmitoylated in Cys 447 or 451 in human or mouse, respectively, by DHHC7 and DHHC21 enzymes. ERα is associated with caveolin 1 protein in the Golgi, and transported to caveolae rafts in the membrane [10,11]. Hence, the downregulation of ERα decreases the detection of E2 binding in the membrane. The extranuclear localization of ERα has been evidenced by immunohistochemical analysis, and also confirmed by the detection of exogenous ERα expression both in the nucleus as well as in the membrane. Furthermore, ERα isoforms (ERα 46 and 36) were also found membrane-associated in human endothelial cells and breast cancer cells [12–17]. Interestingly, mice that express ERα in the membrane (by containing only the LBD), but not in the nucleus, show suppressed lipid synthesis in the liver and adipocytes. Additionally, the studies with these mouse models showed that when ERα is expressed only in the membrane, the transcription of a vast number of genes is decreased, while it is so only for few genes when ERα is expressed exclusively in the nucleus (by mutating the palmitoylation site of the ERα). These data suggest the critical role of nuclear ERα in the expression of several genes, and the implications of extranuclear ERα signaling in the regulation of certain genes linked to lipid metabolism [18–21]. It is also known the activation of extranuclear ERα and ERβ by E2 to regulate the glucose metabolism, stimulating the glycolytic pathways when the glucose concentration is enhanced, or promoting alternative pathways of glucose metabolism under stress conditions when glucose concentration is reduced [22,23]. Likewise, AR has extranuclear activity in the B-cells of pancreatic islets through cAMP production and protein kinase A activation to increase the action of GLP-1(glucagon-like peptide-1) on glucose-stimulated insulin secretion [24]. In addition, membrane-associated ERβ signaling also has a preventive effect against hypertrophy and fibrosis of cardiac tissue [25,26].

Therefore, the mechanisms that control their distribution outside of the nucleus could directly affect associated signaling cascades and the