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Review

Intracellular localization and nucleocytoplasmic trafficking of steroid receptors: An overview

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Abstract

Subcellular compartmentalization and dynamic movements of steroid receptors are major steps in executing their transcription regulatory function. Though significant progress has been made in understanding the mechanisms underlying nuclear import of NLS-bearing proteins, our general and mechanistic understanding about the nuclear export processes has begun to emerge only recently. The discovery of most commonly utilized CRM1/exportin1[1] dependent nuclear export pathway is attributed to a potent nuclear export inhibitor leptomycin B that helped dissecting this and other nuclear export pathways. Simultaneously, utilization of green fluorescent protein (GFP)-tagged intracellular steroid receptors has contributed to not only resolving controversial issue of subcellular localization of unliganded hormone receptors but also provided further insight into finer details of receptor dynamics in living cells. With judicious use of leptomycin B and expression of GFP-tagged receptors in living cells, existence of exportin1/CRM1 independent pathway(s), nuclear export signals and receptors for bi-directional translocation that are unique to steroid receptor trafficking have been specified. Currently, we appear to be arriving at a consensus that steroid/nuclear receptors follow dynamic nucleocytoplasmic processes that deviate from the ones commonly utilized by majority of other proteins.

Keywords: Importin; Exportin1; CRM1; Leptomycin; Steroid receptors; Nucleocytoplasmic shuttling

Contents

1. Introduction

Steroid hormone receptors, the members of superfamily of nuclear hormone receptor (NHR), are transcription factors that regulate gene expression in response to their cognate ligands and have profound effects not only on normal physiology but also immense relevance in a number of human diseases (Pratt and Toft, 1997; Cheng and Balk, 2003). Other than steroid receptors, this superfamily of NHR also includes the receptors for thyroid hormone, retinoic acid, Vitamin D and numerous orphan receptors whose cognate ligands are not known. These hormone receptors are structurally characterized by three distinct domains, i.e., an amino-terminal transactivation domain, a

[1] Exportin1 and CRM1 (chromosome region maintenance 1) are synonyms and for convenience reasons the term 'exportin1' are used throughout the text.

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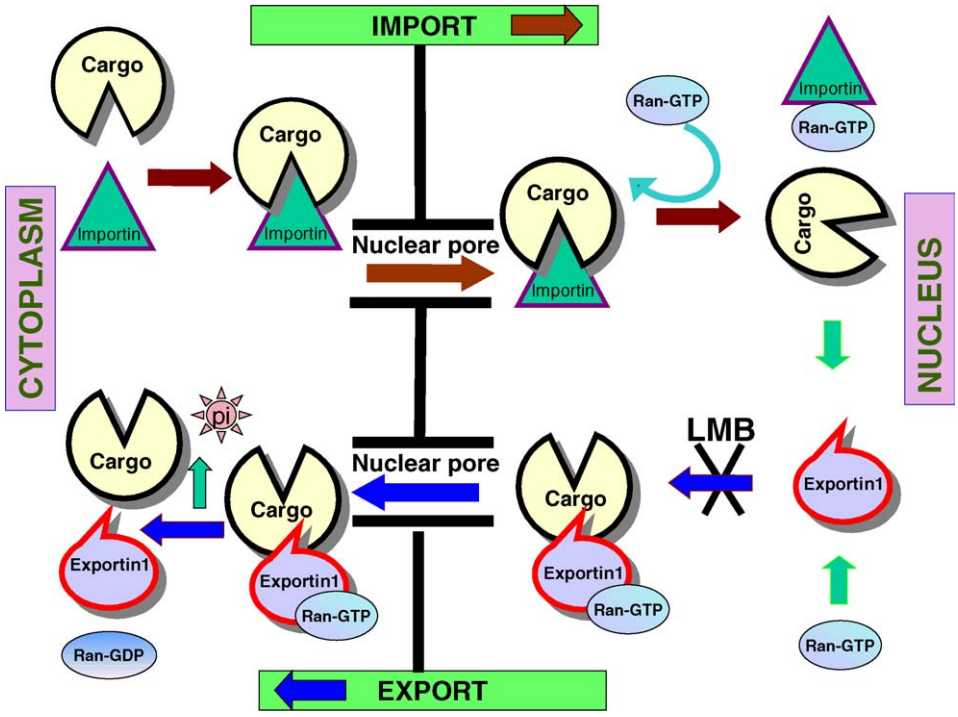

Fig. 1. A simplified model of classical nuclear import and nuclear export pathway for signal-bearing proteins.

central DNA-binding domain, and a carboxy-terminal ligand-binding domain. Since these transcription factors share major structural and functional similarities with each other, the information obtained from one can be applicable to other receptors in the family.

The ability to localize and translocate proteins to specific compartments is fundamental to organization and functioning of all living cells. Although a major share of the newly synthesized proteins in a cell remains in the cytoplasm, distinct sets of proteins need to be incorporated into specific membranes or translocated across these membranes. Eukaryotic cells are characterized by distinct nuclear and cytoplasmic compartments separated by a double membrane nuclear envelope bearing nuclear pore complexes and these pores allow exchange of macromolecules between the two compartments. Fig. 1 shows a simplified model of nuclear import and nuclear export of signal-bearing proteins that transverse the nuclear pore via two classical pathways (reviewed in Gorlich and Kutay, 1999; Sweitzer et al., 2000; Macara, 2001; Lyman et al., 2002; Weis, 2003). In this context, subcellular localization and dynamic movements of transcription factors have been shown to be one of the major means of regulating their transcriptional activity (DeFranco, 2002). The confinement of transcription and translation processes into distinct compartments is considered an ideal strategy for modulating these dynamic events (Black and Paschal, 2004). Several groups have shown that steroid/nuclear hormone receptors continuously shuttle between the cytoplasm and the nucleus (Black et al., 2001; DeFranco, 2002) and the steady state localization of a nucleocytoplasmic shuttling protein is a consequence of a fine balance between operational strengths of ‘nuclear localization signal’ (NLS) and ‘nuclear export signal’ (NES). The regulation of gene expression by steroid/nuclear hormone receptors is modulated mainly through the subcellular compartmentalization of liganded or unliganded receptors. This review provides an overview of the recent advances and emerging perspectives in this exciting area of research.

2. Diverse subcellular localization of steroid receptors

In principle, all intracellular steroid hormone receptors when bound to their natural ligands are nuclear and transcriptionally active; however, subcellular localization of unliganded receptors has been disputed for a long time (see references cited in Table 1). Earlier studies that were based on methods involving cell homogenization, fractionation and immunocytochemistry of fixed cells and tissues resulted in controversial reports. With the advent of advanced technologies and refinement of the pre-existing ones, a consensus appears to have been reached. Presently, the name ‘nuclear receptor superfamily’ appears to be a misnomer since steroid receptors appear to have differential localization patterns depending on their transcriptional behaviour. For example, unliganded glucocorticoid receptor (GR) and androgen receptor (AR) are believed to be predominantly cytoplasmic while mineralocorticoid receptor (MR) is uniformly distributed between cytoplasmic and nuclear compartment (Htun et al., 1996; Fejes-Toth et al., 1998; Tyagi et al., 2000). Both, progesterone receptor (PR) and estrogen receptor (ER) are predominantly nuclear irrespective of their unliganded or liganded state (Lim et al., 1999; Htun et al., 1999; Stenoien et al., 2000). Interestingly, steroid receptor localization has also been extended to mitochondria (Scheller et al., 2003; Yang et al., 2004) and plasma membrane