Preface

Signaling via Nuclear-Localized Transmembrane Receptors: New Homes and New Tasks for Cell Surface Proteins

Growth factor receptors and G protein-coupled receptors (GPCRs) are now known to be present on nuclear or perinuclear membranes, challenging a long-held paradigm regarding their sites of action being restricted to the cell surface membranes (reviewed in refs. 1–4). These observations have led to the concept of intracrine signaling. Intracrine signaling refers to processes whereby ligands, originating within a target cell or taken up from the extracellular milieu, act upon intracellular receptors (reviewed in refs. 3–11). Studies to date have localized Ang II type 1 (AT1R) and type 2 (AT2R) [12–14], bradykinin B2 (15), α- [16, 17] and β-adrenergic [18–20], type B endothelin (ETB) [21, 22], epidermal growth factor (EGF-R) [23], c-erbB-4 [24], insulin [25, 26], interferon β [27], muscarinic cholinergic [28], nerve growth factor [29], prostaglandin E_2 (PGE_2) [30, 31], lysophosphatidic acid type-1 [32], urotensin II [33, 34], and opioid [35] receptors to the nuclear membrane. Consistent with a nuclear location, several GPCRs have now been shown to contain a nuclear localization sequence (NLS) [17, 36–38]. At present, little is known concerning the function of nuclear growth factor receptors or GPCRs: potential roles include regulation of nuclear transport, transcription, and nuclear envelope formation.

Of course, growth factor receptors and GPCRs require the presence of a host of effector molecules in order to transduce signals. Key components of various signaling pathways are also present at the nuclear envelope or within the nucleus itself. These include heterotrimeric G proteins [13, 18, 39, 40] (reviewed in ref. 4), adenylyl cyclase [41], phosphodiesterase [42], diacylglycerol kinase-ζ [43], endothelial nitric oxide synthase (eNOS) [20], phospholipase A_2 [44], phospholipase C-β1 [45, 46], phospholipase D [47–49], phosphatidylinositol 3-kinase C2α [50], RGS proteins (reviewed in ref. 51), β-arrestin1 [52, 53], and G protein-coupled receptor kinases [54–56]. Nuclear membranes also contain sarco/endoplasmic Ca^{2+}-ATPase (SERCA) pumps [57, 58] as well as ryanodine-sensitive (RyR) [58, 59] and inositol trisphosphate-sensitive (IP_3R) [59, 60] Ca^{2+} channels. Hence, the nuclear cisternae are able to accumulate and release Ca^{2+} (reviewed in ref. 61). Furthermore, numerous protein kinases localize to the nucleus, or translocate into or out of the nucleus upon activation [62–66] and inhibition of ERK, p38α/β, PKB, PKG, or JNK inhibited both basal and/or isoproterenol-stimulated transcription in isolated nuclei [19, 20]. Thus, there is evidence supporting the presence and physiological relevance of GPCR signaling at the nuclear membrane.

For intracellular GPCRs to be of functional relevance, barring constitutive receptor activity, there must be a source of the intracellular ligand, whether it be taken up from the extracellular milieu or synthesized within the target cell (reviewed in ref. 3). Ligand-mediated receptor internalization and translocation to the nucleus have been demonstrated for AT1R [37] and EGF-R [67]. In contrast, PGE_2 and catecholamines are taken up by specific transporters [16, 68, 69]. When fluorescent ET-1 or ET-3 analogs were applied extracellularly, they were endocytosed and subsequently trafficked to lysosomes [22, 70], suggesting that endogenous endothelins may serve as ligands for nuclear ETB.

The nuclear envelope (NE) is a double-lipid bilayer structure, comprising inner (INM) and outer (ONM) nuclear membranes, that separates the nucleoplasm from the cytoplasm. The INM and ONM only meet at the nuclear pore: a large complex (>1,000 subunits) that facilitates the regulated exchange of macromolecules and RNA between the nucleoplasm and cytoplasm. The space between the INM and ONM is known as the nuclear cisternae or perinuclear space [71]. The ONM is contiguous with the sarco/endoplasmic reticulum whereas the INM is associated with the nucleoskeleton, a structure analogous to the cytoskeleton, that lines the inner surface of the INM. Furthermore, in adult cardiac myocytes, the sarcoplasmic reticulum and perinuclear space are interconnected [72]. By virtue of the linker of nucleoskeleton and cytoskeleton (LINC) complex, the nucleus is mechanically coupled to the cell surface and extracellular matrix (reviewed in ref. [73]). The LINC complex, comprising the SUN proteins (Sad1p/UNC-84) in the INM and the nesprins at the ONM, has been implicated both in nuclear morphology, positioning, and integrity and in mediating the effects of biomechanical load on gene expression [74]. Lamins A/C and B make up the nucleoskeleton and are coupled to the LINC complex via a direct interaction with SUN proteins. Furthermore, even isolated nuclei are capable of altering their stiffness in response to changes in mechanical force, or tension, and this is thought to involve a phosphorylation-dependent increase in coupling between lamins and the LINC complex [75]. However, it is also becoming increasingly apparent that the nuclear envelope itself is not just a barrier, but plays a role in signaling that may be as complex as that of the cell membrane. The objective of this installment in the series *Methods in Molecular Biology* is to highlight some of the methodologies used to identify and study signal process located in the nuclear membranes.

During their biosynthesis, as a result of an integral N-terminal signal motif, GPCRs orient within membranes with their effector binding site oriented towards the cytoplasm. Hence, whether a receptor is present on either the INM or the ONM, the ligand-binding site will likely be oriented towards the nuclear cisternae. It remains to be determined whether these receptors signal into either the cytoplasm, the nucleoplasm, or both. Hence, whether the receptor is on the INM, the ONM, or both, a significant issue remains—How would an intracrine ligand reach its binding site within the nuclear cisternae? The choices include (1) passive or active transit across the INM or ONM or (2) direct delivery to the nuclear cisternae during biosynthesis. This latter mechanism could include transport from the ER lumen to the nuclear cisternae: the SR and nuclear are interconnected in cardiac myocytes [72] and perhaps this connectivity permits protein trafficking. Alternatively, peptide ligands may arrive at the nucleus by microsomal transport. The nuclear envelope was recently shown to undergo budding [76]; hence, microsomes may also be able to fuse with the ONM and thus deliver their cargo into the perinuclear space.

Nuclear localization has been reported for many peptide ligands (e.g., Ang II, epidermal growth factor, insulin, platelet-derived growth factor, nerve growth factor, parathyroid hormone-related protein, prolactin, interleukin 1, somatostatin, fibroblast growth factors 1 and 2, and TGFα). Hence, the actual source of the intracrine ligand as well as the means whereby it is trafficked to its site of action within the nuclear cisternae may be distinct for each ligand, or class of ligands. Hence, intracrine signaling represents a potentially novel target for therapeutic intervention.

In this volume, we bring together a number of conceptual and methodological aspects important for the validation and characterization of intracrine signaling systems. To date, the best characterized intracrine signaling system is that of angiotensin II (Ang II). AT1R and AT2R have been demonstrated on the nuclear membranes in cardiomyocytes [3],

hepatocytes, and vascular smooth muscle cell lines [13, 77]. In the first chapter of this book, Re and Cook recount the history of Ang II intracrine signaling. How to target such receptors to understand their physiology is the focus of the next several chapters. Internal receptors can be targeted by direct ligand injection into cells (Merlen and Ledoux, Chapter 2), and the use of caged ligands that can be released by UV irradiation to study nuclear GPCR signaling in an intact cell context (Chatenet et al., Chapter 3 and Merlen et al., Chapter 4). Exploring potential sources of ligands and measuring their uptake and delivery to the nucleus are the subject of Dahl et al., Chapter 5. Another interesting possibility for intracrine signaling is the association of the enzyme responsible for ligand synthesis with the receptor for the ligand in question as recently demonstrated for the prostaglandin D_2 DP1 receptor and the intracellular l-prostaglandin D synthase [78]. In this volume, Binda and Parent provide guidance as to how to identify and characterize such interactions with endogenous proteins (Chapter 6).

Methodology to study the subcellular localization and function of GPCRs and other signaling systems is provided in several chapters. Both Tadevosyan et al. (Chapter 7) and Bhosle et al. (Chapter 8) describe techniques to isolate nuclei and localize signaling molecules to this compartment. GPCRs, as discussed above, are not the only receptor family expressed on the nuclear membrane and biochemical techniques to further fractionate inner and outer nuclear membranes are critical tools to understand their trafficking and function (Wang et al., Chapter 9). Another critical issue for the study of intracrine signaling is the requirement to study these systems in native cells to avoid artifacts associated with overexpression. Jong and O'Malley describe methods to study nuclear GPCR signaling in neurons (Chapter 10) and the intact cardiomyocyte is the focus of a number of chapters (Merlin and Allen, Chapter 5; Ryall and Saucerman, Chapter 11; Ljuboyevic and Bers, Chapter 12; and Bossuyt and Bers, Chapter 13).

In addition, numerous chapters focus on methods designed to understand signaling mediated by nuclear and other internal GPCRs. Ryall and Saucerman (Chapter 5) use a high-content microscopy approach to examine phenotypic changes in neonatal cardiomyocytes, an approach that will be generally amenable to studying nuclear GPCR and RTK signaling in the intact cell context. Studying signaling in isolated nuclei has been the focus of many of the studies cited above. It has become clear that nuclear GPCRs control gene expression, and Vaniotis et al. (Chapter 14) describe methods to assess and validate how these receptors modulate transcription using transcription initiation assays, gene arrays, and qPCR. The connections between nuclear GPCRs, G proteins, and their effectors remain incompletely understood. It may be that signals from surface GPCRs and their associated G protein-dependent pathways may integrate with those from nuclear-localized signaling complexes as well as with receptor-independent G protein signaling. Thus, Campden et al. (Chapter 15) demonstrate an unbiased method of identifying nuclear G protein-interacting proteins in order to begin to characterize these integrated networks. As discussed, the nuclear membrane is not the only endomembrane site where GPCR signaling occurs, as described by Calebiro et al. (Chapter 16). Finally, methods are described to study the formation of second messengers such as cAMP and to study the trafficking of receptors from the cell surface (Calebiro et al., Chapter 16). Together, we incorporate a number of state-of-the-art approaches to characterize what is becoming a common theme in cellular signaling.

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