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THEMED ISSUE REVIEW

Structural and molecular determinants of mineralocorticoid receptor signalling

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During the past decades, the mineralocorticoid receptor (MR) has evolved from a much-overlooked member of the steroid hormone receptor family to an important player, not only in volume and electrolyte homeostasis but also in pathological changes occurring in an increasing number of tissues, especially the renal and cardiovascular systems. Simultaneously, a wealth of information about the structure, interaction partners and chromatin requirements for genomic signalling of steroid hormone receptors became available. However, much of the information for the MR has been deduced from studies of other family members and there is still a lack of knowledge about MR-specific features in ligand binding, chromatin remodelling, co-factor interactions and general MR specificity-conferring mechanisms that can completely explain the differences in pathophysiological function between MR and its closest relative, the glucocorticoid receptor. This review aims to give an overview of the current knowledge of MR structure, signalling and co-factors modulating its activity.

KEYWORDS
aldosterone, corticosteroid receptors, glucocorticoids, nuclear receptors

Abbreviations: AR, androgen receptor; BK, large conductance voltage- and Ca^{2+}-regulated K^+ channel; CBP, CREB-binding protein; CNKSR3, connector enhancer of kinase suppressor of ras 3; CRM1, chromosome region maintenance 1; CTE, C-terminal extension; DBD, DNA-binding domain; D-loop, dimerization loop; DOC, deoxycorticosterone; ELL, eleven-nineteen lysine-rich leukaemia; ENaC, epithelial Na^+ channel; FKBP, FK506-binding protein; GEMIN4, Gem-associated protein 4; GILZ, glucocorticoid-induced leucine zipper; GR, glucocorticoid receptor; GRE, glucocorticoid response element; HDAC, histone deacetylase; hGR, human glucocorticoid receptor; hMR, human mineralocorticoid receptor; HOP, Hsp70–Hsp90-organizing protein; HRE, hormone response element; HSD, 11β-hydroxysteroid dehydrogenase; HSP, heat-shock protein; IGF1R, insulin-like growth factor 1 receptor; IP_3, inositol 1,4,5-trisphosphate; KS-WNK1, kidney-specific with-no-lysine kinase 1; LBD, ligand-binding domain; MR, mineralocorticoid receptor; NAD^+, nicotinamide adenine dinucleotide; NCoR, nuclear receptor co-repressor; NHE, Na^+/H^+ exchanger; NLS, nuclear localization signal; NR3, nuclear receptor subfamily 3; NTD, N-terminal domain; PDGFR, PDGF receptor; PER1, period circadian regulator 1; PGC1-α, PPARγ coactivator α; PHA, pseudohypoaldosteronism; PIAS1, protein inhibitor of activated STAT 1; PIM3, proviral integration site of Moloney murine leukaemia virus 3 kinase; PP5, protein phosphatase 5; PR, progesterone receptor; PTM, post-translational modification; S, Svedberg sedimentation rate unit; SGK1, serum- and glucocorticoid-regulated kinase 1; SMRT, silencing mediator of retinoic acid and thyroid hormone receptor; SRC, steroid receptor co-regulator; TRP, tetratricopeptide repeat; Usp2–45, ubiquitin-specific protease 2–45.

1 | INTRODUCTION

The **mineralocorticoid receptor** (MR) is a classical steroid hormone receptor and belongs to the **nuclear receptor subfamily 3** (NR3), which also includes the **glucocorticoid receptor** (GR), the **progesterone receptor** (PR), the **oestrogen receptor** (ER) and the **androgen receptor** (AR). They share a common protein domain structure, first proposed by Green and Chambon (1987). This structure includes three principal domains: the N-terminal domain (NTD), the DNA-binding domain (DBD) and the ligand-binding domain (LBD). In addition, steroid receptors mainly reside in the cytoplasm in their inactive form and function as ligand-activated transcription factors (Figure 1). The MR is highly conserved and the DBD of the zebrafish and the human MR (hMR) share 97% identity, whereas the LBDs share 77% and the NTDs 33% (Fuller et al., 2019). The increasing awareness of functional effects of steroid receptors in health and disease merits increased research of the molecular and structural signalling of the individual receptors. Increasing the understanding of the relationship between structure and function of the MR domains is required for more specific pharmacological modulation of MR activity and for optimizing experimental models and interpreting data from other species.

2 | MR EVOLUTION, EXPRESSION AND FUNCTION

Over 450 million years ago, the MR and the GR both evolved by gene duplication from a common ancestral corticosteroid receptor and a distinct MR is first found in cartilaginous fishes (Bridgham et al., 2006). In the beginning, **11-deoxycorticosterone**, glucocorticoids and **progesterone** occur as natural agonistic ligands for both receptors (Baker & Katsu, 2017; Sturm et al., 2005) and MR seems to play a role in ontogenesis. A switch from agonism to antagonism for progesterone corresponds to the appearance of **aldosterone** synthesis. Aldosterone as a specific ligand for MR developed first in lungfish and later in amphibians and reptiles and has become the MR-specific ligand in all terrestrial vertebrates, for whom conserving water and sodium is of special relevance (Joss et al., 1994; Katsu et al., 2018; Rossier et al., 2015).

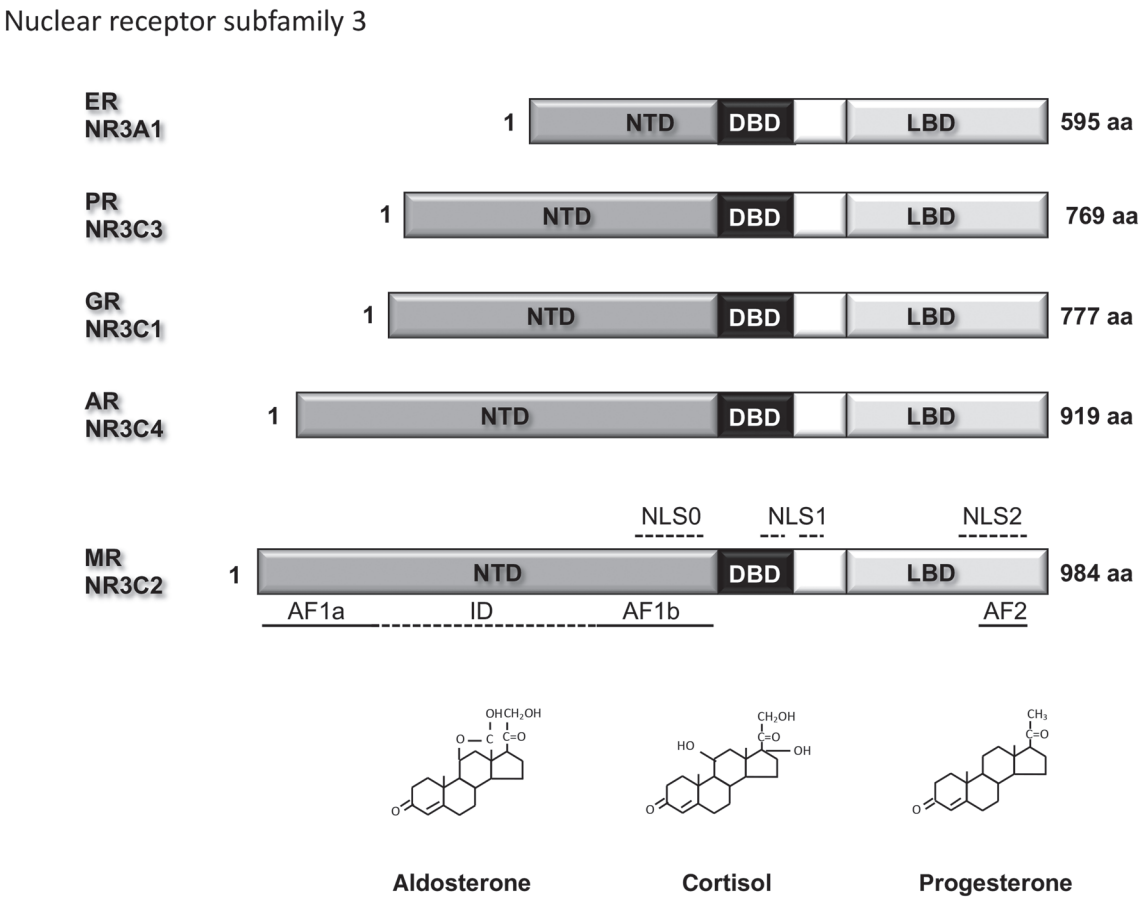

FIGURE 1 Schematic representation of the NR3 subfamily of nuclear receptors. Receptor abbreviations and gene names are indicated on the left. AR, androgen receptor; ER, oestrogen receptor; GR, glucocorticoid receptor; MR, mineralocorticoid receptor; PR, progesterone receptor. Receptor domains are indicated: DBD, DNA-binding domain; LBD, ligand-binding domain; NTD, N-terminal domain; aa, amino acids. Chemical structures for the three main endogenous MR ligands are also included

The MR is expressed in many tissues, such as the classical epithelial target tissues – the gastrointestinal tract (especially colon) and kidney (especially collecting duct) as well as salivary and sweat glands - where its main task is sodium and water retention, together with potassium and proton secretion (Ronzaud et al., 2007). In terms of systemic effects, its action in the kidney regulates long-term volume and BP homeostasis. However, the MR can also participate in pathological kidney disorders. Additionally, the MR is also expressed in numerous non-epithelial target tissues, where its function is more complex but often is associated with inflammation and ROS production. Tissues of high pathological relevance include vasculature (endothelium and smooth muscle) and heart, where the MR induces vasoconstriction, endothelial dysfunction, hypertrophy, fibrosis and atherosclerotic plaque formation. MR antagonists provide effective treatments in patients with different types of heart failure (Pitt et al., 2003; Pitt et al., 2014). Metabolic tissues like adipose tissue, muscle, liver and pancreas also express MR (Feraco et al., 2020; Kuhn & Lombes, 2013). In adipose tissue, activation of MR leads to physiological differentiation and maturation of adipocytes and pathological expansion of white adipose tissue with enhanced adipokine secretion and insulin resistance. Conversely, MR antagonists support browning of white adipose tissue and activate brown interscapular tissue (Greco et al., 2021). Likewise, MR agonists can impair insulin sensitivity and secretion in skeletal muscle and pancreas, respectively. In the liver, MR may play a role in fibrosis and steatosis, but the functional relevance of MR in hepatocytes is still under debate (Matono et al., 2010; Wada et al., 2010). Immune cells also express MR and these play roles in the inflammatory processes in different tissues. Recently, additional MR-expressing tissues, such as skin and retina, have emerged as pathophysiologically interesting targets (Behar-Cohen & Zhao, 2016; Sevilla & Perez, 2018). The MR is also expressed in the CNS and plays an important role in regulating salt appetite and stress response and influences cognitive and emotional function in health and disease (Joels & de Kloet, 2017; Wingenfeld & Otte, 2019). MR expression was also reported in the inner ear (Furuta et al., 1994; Pitovski et al., 1993).

3 | AGONISTS

Different steroid hormones can interact with the MR, namely, mineralocorticoids like aldosterone and deoxycorticosterone (DOC), but also glucocorticoids like **cortisol** or, in rodents, **corticosterone**. Aldosterone, cortisol, DOC and corticosterone all have similar K_D values for human or rodent MR (Arriza et al., 1987; Krozowski & Funder, 1983; Myles & Funder, 1994; Rupprecht et al., 1993). In vitro binding and gene transactivation experiments suggest that MR agonists with similar affinities for the receptor do not induce the same transactivation activity (Hellal-Levy et al., 1999; Hellal-Levy et al., 2000). Instead, the kinetics of the dissociation of the ligand from the receptor seems to be a key characteristic that determines MR stability, cofactor recruitment and overall activity (Hellal-Levy et al., 1999; Hellal-Levy et al., 2000). Although the LBD of the MR is not strictly selective for mineralocorticoids, tissue and context-dependent ligand specificity is achieved by a pre-receptor enzyme, 11β-hydroxysteroid dehydrogenase (HSD), which exists as two isoforms. **HSD1** is a bidirectional NADPH-dependent enzyme, and **HSD2** is a NAD^+-dependent glucocorticoid-inactivating enzyme (Chapman et al., 2013; Edwards et al., 1988; Funder et al., 1988). Consequently, depending on the presence of HSD in the respective tissues, either mineralocorticoids or glucocorticoids are the main activators of the receptor. In classical epithelial target tissues, HSD2 is expressed in close vicinity to the MR and inactivates glucocorticoids to enable selective binding of mineralocorticoids to the MR. In macrophages, cardiomyocytes and some CNS regions, no HSD2 is present and thus glucocorticoids are considered the main ligand. HSD1 plays a role in glucocorticoid regeneration and is expressed primarily in tissues with high sensitivity to glucocorticoids like liver, adipose tissue, certain brain areas and lung (Seckl & Walker, 2001). In classical epithelial target tissues, the response to aldosterone and cortisol appear to be equal, if HSD2 activity is inhibited. In non-classical tissues, this is less clear with sometimes opposing effects being described for different ligands in brain and heart (Mihailidou & Funder, 2005; Rossier et al., 2008; Sato & Funder, 1996; Young et al., 1994). For example, in the CNS, Gomez-Sanchez et al. (1990) found that intracerebroventricular infusion of aldosterone could be blocked by MR antagonists and by corticosterone. Trapp and Holsboer (1995) reported that aldosterone-bound MR is more resistant to proteolysis than cortisol-bound MR, suggesting that the ligands lead to distinct conformational changes. Besides being activated by agonists, ligand-independent stimulation of the MR by **Rac-1**, a small GTPase belonging to the Rho family, has been shown in vivo and in vitro and has been implicated in chronic renal and cardiovascular diseases (Nagase et al., 2012; Shibata et al., 2008), but the exact molecular mechanism remains obscure.

4 | ANTAGONISTS

Progesterone is another endogenous steroid hormone that binds to the MR with high affinity but acts as a competitive antagonist in vertebrates (Arriza et al., 1987; Myles & Funder, 1996; Rupprecht et al., 1993). The physiology of the antagonism of progesterone at the MR in humans is poorly understood. Interestingly, it is the reason for a significant amelioration of the hypertension of individuals with primary aldosteronism during pregnancy. For the agonistic/antagonistic properties of ligands, Thr870 in the LBD of hMR is of special importance and is conserved in most terrestrial vertebrates except for rodents, who possess a Ser at this position. Leu, which is the amino acid at the corresponding position in fish, enables progesterone to act as an agonist (Fuller et al., 2019; Fuller et al., 2021). Important clinical antagonists like the MR inhibitors **spironolactone** and **eplerenone** are based on the basic structure of progesterone. **Drospirenone**, a progestin used in contraceptive medication, is also known for its anti-mineralocorticoid effects (Oelkers, 2004). Interestingly, a mutation of Leu to Ser at position 810 of the LBD of the MR changes

progesterone (and spironolactone) from an antagonist to an agonist with early-onset severe hypertension, despite low levels of aldosterone (Geller et al., 2000). A new class of MR antagonists is derived from dihydropyridine-based compounds, such as **finerenone** or **esaxerenone** (Bakris et al., 2020; Pitt et al., 2021). They are MR-selective and have a high potency but may have fewer side effects. Additionally, these non-steroidal MR antagonists retain their antagonism in the Ser810 mutant and in the fish MR, which has Leu870.

In large clinical trials, MR antagonists were effective in lowering mortality and hospitalization rate in patients with severe heart failure with reduced ejection fraction (RALES) or after acute myocardial infarction complicated by left ventricular dysfunction (EPHESUS) but also in certain patient groups with preserved ejection fraction (TOPCAT) (Pfeffer et al., 2015). A significant improvement in cardiovascular outcome was also achieved in patients with mildly symptomatic left ventricular systolic dysfunction (EMPHASIS-HF) (Zannad et al., 2010). In patients with Type 2 diabetes with chronic kidney disease, MR antagonists resulted in a lower risk of chronic kidney disease progression, an improvement in cardiovascular outcomes (FIDELIO-DKD, FIGARO-DKD) (Bakris et al., 2020; Filippatos et al., 2021; Pitt et al., 2021). Proteomics analyses of biomarkers in plasma suggest that MR antagonists lead to a reduction of collagen metabolism, **brain natriuretic peptides**, inflammation and thrombosis and an increase in levels of adipokines, markers of haemostasis maintenance, insulin suppression and inflammatory regulation (Ferreira et al., 2021).

5 | GENE STRUCTURE AND EXPRESSION REGULATION

hMR is encoded by gene *NR3C2*, which contains eight coding exons spanning approximately 370 kb of chromosome 4 q31.23 region (NCBI *Homo sapiens* Updated Annotation Release 109.20200815). Exon organization of *NR3C2* matches MR protein modular organization: exon 2 codes for the NTD; exons 3 and 4 code for the DBD domain; and exons 5–9 code for the LBD. The full-length, most abundant transcript produces a protein of 984 amino acids. Two alternative promoters and alternative splicing produce different transcripts that are generally less abundant than the canonical form. Interestingly, some of these transcripts have a truncated steroid-binding domain and can either potentiate MR signalling (Zennaro et al., 2001) or act as dominant-negative regulators (Lema et al., 2017) of the full-length MR. Two additional isoforms due to alternative translation initiation sites have been proposed (Pascual-Le Tallec et al., 2004), but their existence in vivo has not been demonstrated. In general, the biological relevance of MR isoforms is unclear, although it has been recently suggested that one of them acts as a general brake on MR signalling, which is released during hypotonic stress in the kidney (Lema et al., 2017). The 5′ flanking region of the first two non-coding exons in human *NR3C2* were identified as functional promoters and named P1 and P2. A target oncogenesis approach in mice suggested that P1 drives the expression of MR in vivo in all MR-expressing tissues, whereas P2 possesses lower transcriptional activity and appears to be more important during development (Le Menuet et al., 2000). In addition, there is evidence supporting post-transcriptional regulation of MR synthesis, particularly in response to osmotic challenge. Hypertonic stress potently reduces MR transcript and protein abundance via induction of Tis11b, an mRNA-destabilizing protein that binds to the MR 3′ untranslated region (Viengchareun et al., 2014). The role of microRNAs in regulating MR expression is becoming increasingly clear (Butterworth, 2021).

6 | MR ARCHITECTURE, STRUCTURE AND POST-TRANSLATIONAL MODIFICATIONS

Although the organization of protein domains in MR is well defined, its 3D arrangement has been only partly solved, with separate structures available for the DBD and LBD domains (Hudson, Youn, & Ortlund, 2014). Recently, cryo-electron microscopy techniques have started providing structural information on ER- and AR-coactivator complexes (Yi et al., 2021) and will certainly be essential to understand the dynamic structural rearrangements in MR.

The NTD of MR is an intrinsically disordered region that has been difficult to study from a structural perspective, because its conformation depends on the interacting proteins and not on its primary sequence. The NTD is the most variable region between steroid receptors, with the 602-amino acid MR NTD being the longest in the nuclear receptor superfamily. The divergence of the NTD between steroid receptors and the fact that all except the ER bind a common DNA consensus sequence has led to the hypothesis that the NTD confers most of the specificity in gene transactivation. Of note, MR NTD is also highly variable between mammals and other species. Whereas human and mouse MR NTDs share approximately 90% identity, human and zebrafish NTDs are only 33% identical. This suggests caution when using non-mammalian species for preclinical research involving MR.

The NTD of steroid receptors contains a transcription activation function domain (AF1). In the case of MR, AF1 appears to be a bipartite domain, with two regions that have independent activation functions (AF1a encompassing amino acids1–169 and AF1b amino acids 451–602), separated by a middle domain (amino acids 163–437) with activation or repression functions, which are likely to depend on the interacting co-regulators (Fuse et al., 2000; Pascual-Le Tallec et al., 2003). This organization is similar to that found in the NTD of AR and PR isoform B. Work with AR demonstrated that a ligand-dependent intramolecular interaction between the NTD and the LBD is essential for receptor function (N/C interaction; Langley et al., 1995), a process later shown also for PR and ER. Rogerson and Fuller (2003) proposed that MR, but not GR, also shows an N/C interaction that is selective for aldosterone and, unlike the AR, does not strictly require domain activation function 2 (AF2; see below) in the LBD. This suggests that the structural determinants for N/C interaction in MR are distinct and that this process is not essential for function but may contribute to ligand-specific transcriptional outcomes. The NTD also contains a Ser/Thr-rich nuclear localization signal (NLS) (NLS0, especially amino acids 590–602) (Walther et al., 2005).

The functionality of the NTD is modified by different post-translational modifications (PTMs) that act independently or modify each other in a cell-type-specific manner (Alvarez de la Rosa & Serrano-Morillas, 2019; Gadasheva et al., 2021). These include **ERK1/2**-dependent phosphorylation of six Ser residues with the combined effect of inducing the removal of mono-ubiquitin residues, a process that in turn triggers receptor destabilization (Faresse et al., 2012). Other NTD phosphorylation events include **CDK5**-dependent transcriptional inhibition (Kino et al., 2010) and **casein kinase 2**-dependent potentiation of aldosterone responses (Ruhs, Nolze, et al., 2017). SUMOylation of the NTD has complex functional effects, are promoter dependent and may also include concurrent modification of co-regulators (Alvarez de la Rosa & Serrano-Morillas, 2019; Pascual-Le Tallec et al., 2003; Yokota et al., 2007).

The DBD domain of MR spans amino acids 602 to 677 and at its core is formed by two zinc finger domains that are highly conserved between steroid receptors. The crystal structure of MR DBD forming a complex with a canonical DNA response element (hormone response elements [HREs]) showed a configuration that closely follows that of GR, although with subtle differences in the packing of a key residue (His635 in hMR and His453 in human GR [hGR]) (Hudson, Youn, & Ortlund, 2014). The second zinc finger domain forms the dimerization loop (D-loop), involved in receptor dimerization. The hMR D-loop mutation Cys645Ser produces renal pseudohypoaldosteronism type 1 (PHA1), a human autosomal dominant disorder characterized by resistance to mineralocorticoids, producing electrolyte imbalances (Pujo et al., 2007). Between the two zinc finger domains, there is a short stretch of amino acids named the 'lever arm' (Hudson, Youn, & Ortlund, 2014), which has been extensively studied in GR, where it has been implicated in transducing DNA binding events to the dimerization interface in the D-loop (Meijsing et al., 2009; Watson et al., 2013). The fact that the lever arm is fully conserved in hMR suggests that it plays the same role in both receptors, although subtle differences in their crystal structure may underlie differential effects of DNA binding (Hudson, Youn, & Ortlund, 2014). Interestingly, the mutation Gly633Arg in the MR lever arm reduces MR-mediated transactivation and also produces PHA1 (Sartorato et al., 2003).

The distal part of the DBD contains the C-terminal extension (CTE)/hinge domain, which displays lower sequence conservation between steroid receptors and separates it from the LBD. The CTE contributes to HRE binding by directly interacting with the DNA minor groove (Aagaard et al., 2011). In addition, the hinge domain in GR interacts with transcriptional co-repressors (Hong et al., 2009) and its function is modified by Lys acetylation (Nader et al., 2009), although whether this is the case also for MR remains an open question. Finally, the hinge domain is also important because it contains NLSs (NLS1 with a bipartite basic motif in the case of MR; Walther et al., 2005).

The LBD is a region of 307 amino acids that contains the ligand binding pocket, a transactivation function domain (AF2), an additional dimerization interface, regions involved in the interaction with chaperones and an NLS (NLS2). The LBD adopts a conserved structure of 11 α helices named by convention H1 to H12 (H2 is present in other nuclear receptors, but unstructured in MR) and four β strands distributed into three parallel layers that form a helical sandwich (Bledsoe et al., 2005; Fagart et al., 2005; Li et al., 2005). This structure generates a hydrophobic ligand binding pocket where sequence divergence is higher between nuclear receptors, allowing for specific ligand recognition. At one end of the ligand binding cavity, Gln776 of helix 3 and Arg817 of helix 5 are important residues to establish bonds with the 3-keto-group of MR-binding steroids (Fagart et al., 1998). A naturally occurring missense mutation of Gln776Arg reduces aldosterone-binding capacity of the MR and causes PHA1 (Sartorato, Cluzeaud, et al., 2004). For MR agonists like aldosterone and cortisol, Asn770 in helix 3 is important for interacting with the C21-hydroxyl function. The interactions between the C21-hydroxyl group of agonists and the residues Asn770 and Thr945 are crucial for the stabilization of helix 12 in its active state (Hellal-Levy et al., 2000). An MR-Asn770Ala mutation abolishes binding of agonists to MR, and antagonists like progesterone are also unable to establish this contact (Fagart et al., 1998). With the help of a chimeric MR/GR LBD construct, Rogerson discovered that amino acids 804–874 are required for the binding of aldosterone (Rogerson et al., 2007) and MR transactivation (Rogerson & Fuller, 2003). Amino acids especially critical for ligand binding and specificity reside on the external surface of the LBD (amino acids 820–844) and not in the ligand binding pocket, suggesting that they are involved in interactions with chaperones like heat-shock protein 90 (**HSP90**) that are important for the conformation of unliganded receptors. Alternatively, these residues could be important for allosteric transitions upon ligand binding or for interactions with co-regulators. Phosphorylation of Ser843 in this region leads to inactivation of the MR in intercalated cells of the kidney collecting duct, both by lowering ligand affinity (Shibata et al., 2013) and by uncoupling ligand binding to receptor activation (Jimenez-Canino et al., 2016). Interestingly, mutagenesis experiments revealed that also the C-terminal end (amino acids 975–984), which does not affect HSP90 binding, is crucial for agonist binding (Sartorato, Cluzeaud, et al., 2004). An overview of MR mutations and their functional and clinical effects has been provided by Zennaro and Fernandes-Rosa (2017).

The rest of the LBD displays higher sequence conservation. Importantly, it includes AF2, formed by helices H3, H4, H5 and H12. Upon ligand binding, a conformational change occurs and H12 closes over the binding pocket of the LBD (Bledsoe et al., 2005; Fagart et al., 2005; Li et al., 2005), generating the active conformation, a change common to the other nuclear receptors, which provides a docking platform for transcriptional co-regulators.

7 | CHAPERONES

In its unstimulated state without ligand, the MR predominantly resides in the cytoplasm (Nishi et al., 2004; Piwien Pilipuk et al., 2007), but depending on cell type and context, it can also be equally distributed

between the cytoplasmic and nuclear fractions (Fejes-Toth et al., 1998; Nishi et al., 2001; Tanaka et al., 2005; Walther et al., 2005) or even mostly nuclear in cardiomyocytes with low HSP90 content (Hernandez-Diaz et al., 2010). To ensure a conformation that enables ligand binding and prevents degradation, the MR is associated with a multiprotein complex (Binart et al., 1995; Galigniana, Erlejman, et al., 2010) with a very dynamic structure that constantly assembles and disassembles and changes its composition. The key chaperone molecule in this complex crucial for high affinity binding of ligands to the MR is HSP90 (Binart et al., 1995; Galigniana, Erlejman, et al., 2010; Huyet et al., 2012) with its nucleotide-binding domain that acts as an ATP/ADP switch. When bound to ATP, HSP90 possesses properties for keeping the MR in its correct conformation. Couette et al. (1998) identified amino acids 711–733 at the hinge region and LBD of the hMR as being essential for HSP90 binding. The multiprotein complex includes other chaperones apart from HSP90 - **HSP70**, **protein23** (**p23**) and Hsp70–Hsp90-organizing protein (HOP) - and co-chaperones including tetratricopeptide repeat (TRP)–domain proteins such as FK506-binding proteins (FKBP) and protein phosphatase 5 (PP5) (Figure 2) (Bruner et al., 1997). Two HSP90 together with HSP40, HSP70 and HOP form a complex that is stabilized by p23 (Galigniana, Echeverría, et al., 2010). The complex can then bind to MR, causing release of HOP and association with other TRP-domain possessing co-chaperones such as **FKBP51**, **FKBP52** and PP5 (Bruner et al., 1997), which are not essential for complex assembly or MR stability (Huyet et al., 2012; Rafestin-Oblin et al., 1989). TRP proteins like FKBP51, FKBP52 and PP5 are dynamically exchanged on HSP90 dimers according to the ligand bound to the receptor (Gallo et al., 2007). When aldosterone binds to the MR, the exchange of FKBP51 for FKBP52 is favoured (Galigniana et al., 2002). In the absence of HSP90 or when HSP90 is inhibited, the MR is polyubiquitinated via the E3 ubiquitin ligase CHIP (C-terminus of Hsc70-interacting protein) and degraded in the proteasome (Faresse et al., 2010; Galigniana et al., 2004).

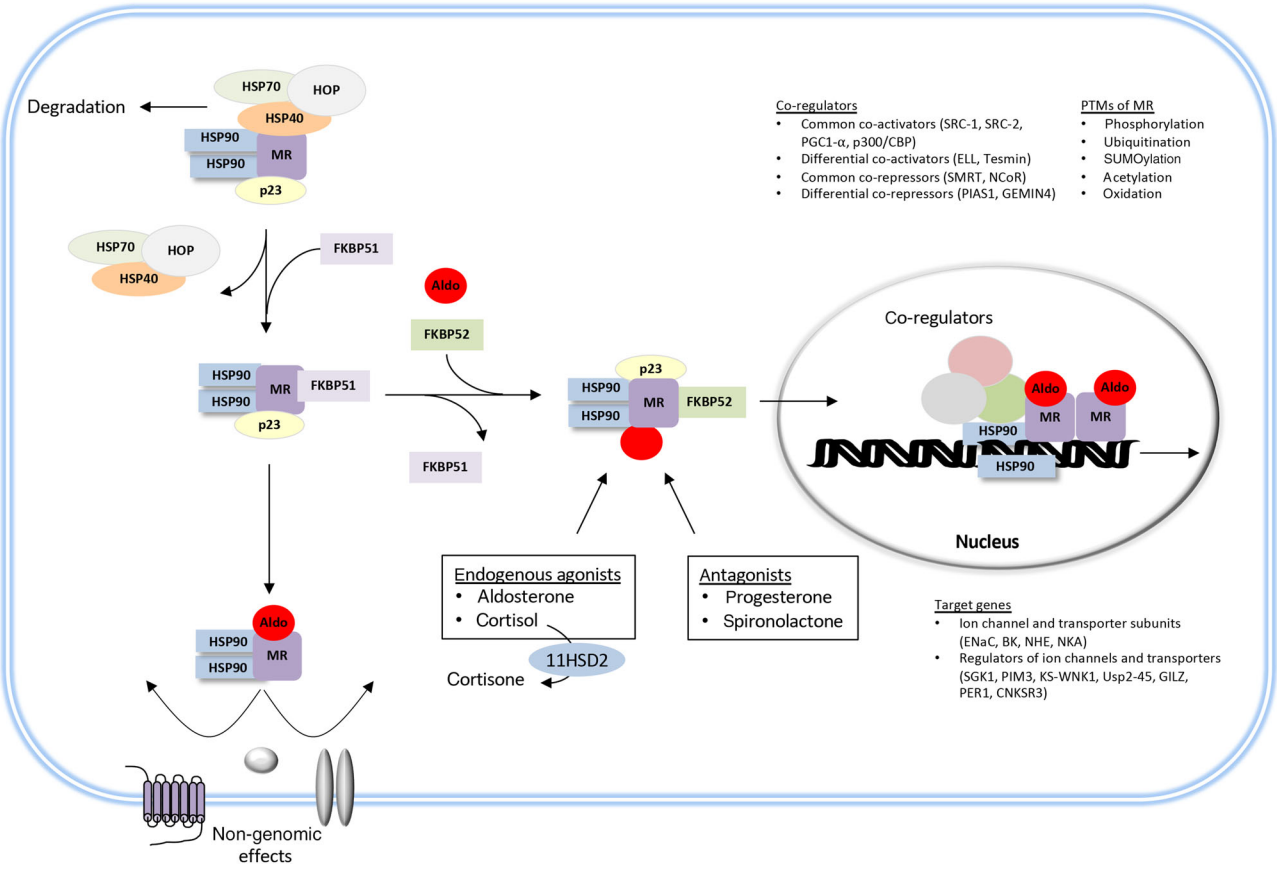

FIGURE 2 Key cellular and molecular events regulating MR action. Examples of MR co-regulators and target genes are provided (see text for references). 11HSD2, 11-β-hydroxy-steroid dehydrogenase type 2; aldo, aldosterone; BK, large conductance voltage- and Ca^{2+}-regulated K^+ channel; CBP, CREB-binding protein; CNKSR3, connector enhancer of kinase suppressor of ras 3; ELL, eleven-nineteen lysine-rich leukaemia; ENaC, epithelial Na^+ channel; FKBP, FK506-binding protein; GEMIN4, Gem-associated protein 4; GILZ, glucocorticoid-induced leucine zipper; HOP, Hsp70–Hsp90 organizing protein; HSP, heat-shock protein; KS-WNK1, kidney-specific with-no-lysine kinase 1; NCoR, nuclear receptor co-repressor; NHE, Na^+/H^+ exchanger; NKA, Na^+,K^+-ATPase; PER1, period circadian regulator 1; PGC1-α, PPAR-γ coactivator-α; PIAS1, protein inhibitor of activated STAT 1; PIM3, proviral integration site of Moloney murine leukaemia virus 3 kinase; SGK1, serum- and glucocorticoid-regulated kinase 1; SMRT, silencing mediator of retinoic acid and thyroid hormone receptor; SRC-1, steroid receptor co-regulator 1; Usp2–45, ubiquitin-specific protease 2–45

8 | LIGAND BINDING

Ligand binding induces a conformational change in the LBD of the MR that enables the interaction with co-regulatory molecules and the formation of new interdomain interactions that are both required for MR activation. Helix 12 is rotated to occlude the binding pocket and helices 3, 5 and 11 are rearranged to form a hydrophobic cleft on the surface of the LBD for recruitment of co-regulators with an LxxLL motif (Bledsoe et al., 2002) to AF2 (Hultman et al., 2005). Some co-regulators interact with AF1 or AF2 only in the presence of agonists but not antagonists and some even have been described as aldosterone-specific (Fuller et al., 2017). Additionally, a protein–protein interaction between the N- and the C-terminus of the MR occurs ligand-specifically. It is strongly promoted by binding of aldosterone and the synthetic MR agonist **9α-fluorocortisol**, and is weak or missing when binding cortisol or antagonists (Rogerson & Fuller, 2003). A correlation between efficiency of inducing the N/C terminal interaction and the ligands' agonistic potency was therefore suggested. For the AR, studies have shown that the N/C interaction is intermolecular rather than intramolecular and may very likely be involved in stabilizing the dimer or multiple MRs at HREs (Langley et al., 1995). Overall, depending on the target tissue investigated, binding of different ligands may result in different changes in MR conformation and thereby interaction partners and thus different outcomes.

9 | NUCLEAR IMPORT

Early low salt density gradient centrifugation analyses indicated that the MR exists as a ≈9S oligomeric HSP90-containing complex in the cytosol, which transforms into a nuclear 4S form (Marver et al., 1972). It was initially proposed that ligand binding causes dissociation of MR from HSP90 and thereby unmasking of an NLS, which then initiated nuclear translocation (Picard & Yamamoto, 1987; Walther et al., 2005). Three NLSs of the MR have been described and characterized (Walther et al., 2005), but no clear relationship between NLS availability and nuclear transport was found. For nuclear localization of unliganded MR, NLS0 seems to be most important but it also appears to contribute to both ligand-independent and -dependent nuclear translocation in a cell-type-specific manner (Hernandez-Diaz et al., 2010). NLS1 in the C terminus of the MR DBD functions together with NLS0 and NLS2 to stimulate nuclear uptake of agonist- or antagonist-treated receptor. NLS2 within the LBD mediates the nuclear transfer of ligand-bound MR, independent of MR co-activator proteins. Several reports indicate that NLS1 is not obscured by HSP90 and that HSP90 remains associated with the receptor during nuclear translocation (Piwien Pilipuk et al., 2007). Several investigators reported that HSP90 is not exclusively located in the cytoplasm but also in the nucleus and that HSP90 inhibitors are able to affect nuclear translocation and transcriptional activity (Galigniana, Erlejman, et al., 2010; Grossmann et al., 2012; Hernandez-Diaz et al., 2010). HSP90 enhances DNA binding of MR without being bound to DNA itself, probably by stabilizing the receptor structure (Bain et al., 2007). Recent data, therefore, suggest that the exchange from FKBP51 to FKBP2 in the multiprotein complex upon ligand binding links MR to dynein/dynactin motor proteins and mediates trafficking along microtubuli to the nucleus (Galigniana, Erlejman, et al., 2010; Grossmann et al., 2012; Piwien Pilipuk et al., 2007).

Transiting the nuclear pore complex for molecules larger than 40 kDa requires the help of importins. Classically, importin-α binds the NLS of a molecule and forms a complex with importin-β that then facilitates transport into the nucleus. Tanaka et al. (2005) demonstrate that intact NLS1 is necessary for the trafficking of MR together with importin-α to the nucleus in COS1 cells. However, importin-β does not change its distribution upon ligand treatment of MR. Because absence of HSP90, inhibition of HSP90 and blocking of NLS1 strongly delay nuclear translocation without completely abolishing it, there is evidence that two types of transport for the MR to the nucleus exist (Galigniana, Erlejman, et al., 2010): One involves NLS1, HSP90, FKBP52, dynein, dynactin and importin-α and is rapid with a half-life time of 4–6 min, and the other is independent of HSP90 but requires NLS2, is based on diffusion and takes much longer with a half-life time of 40–60 min (Piwien Pilipuk et al., 2007; Walther et al., 2005).

10 | NUCLEAR EXPORT

Nuclear export for steroid receptors is less well investigated than nuclear import. For the AR, an atypical, ligand-dependent nuclear export signal was characterized in the LBD. It was necessary and sufficient for the cytoplasmic localization of the AR and did not rely on chromosome region maintenance 1 (CRM1; **exportin 1**). A corresponding structural element was also found in the MR (amino acids 809–883) with only moderate sequence homology (Saporita et al., 2003). For the GR, a nuclear export was reported that takes several hours after steroid withdrawal, is CRM1 independent and relies on 15 amino acids between the two zinc fingers in the DBD (Black et al., 2001). For the MR, in spite of the same 15 amino acid sequence being conserved, no nuclear export could be verified, and it has been suggested that it is an atypical nuclear hormone receptor that moves unidirectionally from the cytoplasm to the nucleus (Walther et al., 2005). A mutant (Gly633Arg) of this putative nuclear export signal displays atypical subcellular trafficking, predominant nuclear retention but also altered interaction with DNA and reduced transactivation activity, but the molecular mechanism for this phenotype is unclear (Sartorato, Khaldi, et al., 2004).

11 | DIMERIZATION

The most common model of steroid receptor activation proposes that ligand binding induces a structural rearrangement of the LBD, triggering a dissociation or remodelling of the receptor–chaperone heterocomplex, promoting homodimerization of the receptor and nuclear translocation (Weikum et al., 2018). In the case of GR, it is

commonly assumed that the LBD provides a larger and stronger dimerization interface than the DBD, although this has not been directly tested in MR. This seems to be a common feature in all oxo-steroid receptors (AR, GR, MR and PR), although a common dimerization interface in the LBD has not been found (Nadal et al., 2017). At least in the case of GR, ligand binding is essential for receptor–DNA interaction, which triggers a conformational change in the DBD, strengthening the D-loop-mediated dimerization, which in turn triggers a conformational change in the LBD, promoting co-regulator recruitment (Presman & Hager, 2017). Whether this process is conserved in MR has not been directly assessed. Homodimerization of MR normally occurs before DNA binding as soon as MR is released from HSP90 (Grossmann et al., 2012). In vitro or under experimental conditions, dimerization can occur independent of DNA and even independent of ligand when applying high salt concentrations (Grossmann et al., 2012; Savory et al., 2001). The MR can also form heterodimers with the GR although the relevance of these still is not clear (Nishi et al., 2004; Savory et al., 2001). Based on FRET experiments with intact MR and GR lacking NLS1, Nishi et al. (2004) suggested a cytosolic heterodimerization, whereas Savory et al. (2001) found a nuclear heterodimerization.

12 | DNA BINDING AND GENE REGULATION

In the nucleus, the MR binds to HREs in the promoter of target genes as dimers (Tsai et al., 1988). Binding of steroid receptors to their HREs involves rapid cycling with the rate of exchange influencing the transcriptional activity and depending on the bound ligand (McNally et al., 2000; Nishi, 2011). HSP90 facilitates binding of MR to DNA and modulates receptor cycling at DNA and possibly also receptor degradation (Freeman & Yamamoto, 2002). In vitro, binding of MR and GR to DNA does not depend on the presence of ligand, but in vivo, no transactivation of GR or MR occurs without ligand or after incubation with an HSP90 inhibitor because no rapid translocation into the nucleus occurs (Grossmann et al., 2012). The MR does not possess specific HREs but reacts with glucocorticoid response elements (GREs), which are also common to GR, AR and PR and typically consist of two MR binding half-sites structured as an inverted palindrome separated by three nucleotides with the consensus sequence AGAACAnnnTGTTCT (Arriza et al., 1987). In vitro, DBDs from MR and GR bind HRE with the same affinity (Hudson, Pickard, et al., 2014). The exact sequence of the DNA binding site and adjacent nucleotides seems to influence the response of steroid receptors and their interaction partners (Meijsing et al., 2009). Additionally, the number of HREs and whether they are single or double can vary in various experimental and natural promoters and affect the response. Besides classical GREs, monomeric, atypical and composite HREs with other transcription factors such as AP-1 and NeuroD have been described (Meinel et al., 2013; Pearce & Yamamoto, 1993; Stow et al., 2009; van Weert et al., 2017). For the GR, transrepression through tethering to other transcription factors via protein–protein interactions or direct binding to other transcription factor DNA binding sites was reported for AP1 and NF-κB (Hudson et al., 2018), and something similar may also be possible for MR.

Systematic studies of the distribution of MR binding sites throughout the genome by chromatin immunoprecipitation are very challenging and have been performed with different results. In a human renal cell line with MR overexpression, Le Billan et al. identified 974 MR binding sites, of which 94% were located more than 10 kb away from transcriptional start sites. Most did not include conserved palindromic GREs but rather only half-sites or other sequences (Le Billan et al., 2015). Furthermore, alternative DNA binding recognition sites for FOX, AP-1, EGF1 and PAX5 were found, mostly not even in combination with a classical GRE. In contrast, 918 unique MR binding sites and 475 combined MR–GR binding sites were identified in rat hippocampus and included mostly canonical GRE sequences (van Weert et al., 2019).

The analysis of MR target genes has been complicated by several factors. It is remarkably tissue specific, a fact well exemplified by the divergent transcriptional regulation of **epithelial Na^+ channel** (**ENaC**) subunits by MR/aldosterone in different tight epithelia. In addition, it is generally difficult to cross-reference nuclear receptor genomic binding sites with regulated genes, because HREs are not always proximal to the gene where they exert their effects. Furthermore, MR activation by glucocorticoids, and the fact that MR and GR share HREs and regulate overlapping gene sets, makes it difficult to clearly dissect the roles of these two nuclear receptors on gene regulation.

Identification of MR target genes has been attempted in different tissues (kidney, cardiovascular) with different techniques (SAGE, microarrays and transcriptomics) and has resulted in a variety of directly or indirectly regulated MR target genes (Fakitsas et al., 2007; Fejes-Toth & Naray-Fejes-Toth, 2007; Latouche et al., 2010; Le Billan et al., 2015; Robert-Nicoud et al., 2001; Sekizawa et al., 2011; Ziera et al., 2009). These studies and others have identified target genes that have a clear physiological role in controlling transepithelial ion transport, including subunits of ion channels and transporters such as ENaC, high-conductance calcium- and voltage-dependent potassium channel (BK), Na^+/H^+ exchanger (NHE) or the Na^+,K^+-ATPase (Figure 2). Other MR targets include regulators of ion transport, including the kinases **SGK1**, **PIM3** or the kidney-specific isoform of with-no-lysine kinase 1 (KS-WNK1), the ubiquitin-specific protease 2–45 (Usp2–45) and other factors such as glucocorticoid-induced leucine zipper (GILZ, also known as TSC22D3), the period circadian regulator 1 (PER1) or the scaffold protein connector enhancer of kinase suppressor of ras 3 (CNKSR3). In addition to these target genes in tight epithelia, MR-regulated transcripts have been identified in many different cell types and tissues, with particular emphasis on abnormal regulation of transcripts in pathophysiological settings. These include transcripts shown to be important in MR roles related to obesity, cardiovascular fibrosis and inflammation, and neuro-psychiatric conditions.

13 | CO-FACTORS

Gene transactivation by nuclear receptors needs the stabilization of an active state of the receptor by ligand binding, which will then

interact with open chromatin in a highly dynamic fashion. A productive nuclear receptor binding event will result in interactions with other transcription factors and recruitment of co-regulators, which induce further chromatin remodelling and the incorporation of a coactivator complex that interacts with RNA polymerase II, enhancing transcription (Aagaard et al., 2011). Because most HREs are away from the transcription start site, nuclear receptor function involves the formation of complex three-dimensional interactions in the genome. These interactions are likely to be affected by nearby or distant transcription factor binding sites. Additional modes of action have been proposed, involving tethering of nuclear receptors to transcription factors already bound to DNA, a process that in the case of GR has been mainly linked to transrepression functions (Aagaard et al., 2011).

Over 400 nuclear receptor co-regulators have been identified, many of which impart cell-type-specific outcomes to nuclear receptor activation, but only a limited amount have been studied in the case of MR (for a recent, detailed review on MR co-regulators, see Fuller et al., 2017). Common co-activators of nuclear receptors, such as steroid receptor co-regulator (SRC)-1, SRC-2 or PPAR-γ coactivator-α (PGC1-α), bind MR AF-2, located in the LBD, through their LxxLL motifs (Fuller et al., 2017), although there is evidence also for LxxLL-independent interaction, most likely via the NTD (Zennaro et al., 2001). Other common co-activators such as p300/CREB-binding protein (CBP) are also able to interact with MR via both the NTD and the LBD (Fischer et al., 2010). MR has also been shown to interact with common nuclear receptor transcriptional co-repressors, such as nuclear receptor co-repressor (NCoR) and silencing mediator of retinoic acid and thyroid hormone receptor (SMRT) (Fuller et al., 2017).

Given the close relationship between GR and MR and the ligand promiscuity shown by the latter, it is assumed that MR- and ligand-specific interactions with co-regulators are essential to explain the receptor pathophysiology. Several attempts have been made to identify such co-regulators. Hultman et al. (2005) deployed a mammalian two-hybrid approach, using MR LBD as bait and a panel of peptides containing the LxxLL motif or the CoRNR box motif found in corepressors as prey. The study did not identify new co-regulators or ligand-specific interactions, although it uncovered mutations in AF2 that selectively abolished cortisol activation, implying ligand-specific LBD conformations. A yeast two-hybrid screening using MR NTD as bait identified ELL (eleven-nineteen lysine-rich leukaemia), an RNA polymerase II elongation factor, as an MR-interacting co-regulator that potentiates MR activity while repressing GR (Pascual-Le Tallec et al., 2005). Other yeast two-hybrid screening studies have identified additional co-regulators (Fuller et al., 2017). Using a phage display strategy, Yang et al. (2015) selected in vitro interacting partners for immobilized, ligand-bound full-length MR, leading to the identification of Gem-associated protein 4 (GEMIN4), which acts as a cell-type-specific MR co-repressor. An additional phage display screening using cDNA libraries from heart and kidney identified other co-regulators, including EEF1A1, SSRP1 and XRCC6 (Yang et al., 2014).

Further studies have identified enzymes that modify MR activity through PTM but may also have overlapping functions as co-regulators, using MR as a docking site to modify other components of chromatin or the transcription machinery. Examples include **histone deacetylases** 3 and 4 (HDAC3–4), which potentiate MR– aldosterone transactivation (Lee et al., 2015). Also, SUMO ligase Ubc9 interacts with the NTD and potentiates MR transactivation, even in the presence of mutations preventing SUMOylation of the receptor (Yokota et al., 2007). Similarly, SUMO ligase protein inhibitor of activated STAT 1 (PIAS1) interacts with MR NTD, in this case acting as an MR selective co-repressor, with no effect on GR (Pascual-Le Tallec et al., 2003). Interestingly, the effect of PIAS1-mediated MR SUMOylation on co-repression is promoter-dependent.

The search for specific co-regulators of MR has focused not only on identifying factors that differentially regulate MR versus GR but also, very importantly, on factors that discriminate between aldosterone and glucocorticoid-induced MR activity. Using a yeast two-hybrid approach with MR LBD as bait, Rogerson et al. (2014) identified the first ligand-specific MR co-activator, Tesmin, also known as MLT5, which specifically potentiates MR– aldosterone-mediated transactivation. MR–Tesmin interaction uses a classic LxxLL motif, and therefore, the structural basis for ligand discrimination remains unknown.

Given the expanding list of MR co-regulators, many of them showing cell type, ligand or promoter specificity, it is tempting to speculate that detailed characterization of these factors could lead to more selective MR modulators that avoid undesired side effects of currently available antagonists. An example of this concept is provided by the effects of HDAC inhibitors on increasing MR acetylation, preventing cardiac hypertrophy and fibrosis in a rat model of hypertension (Kang et al., 2015).

14 | DEGRADATION/INACTIVATION

Detection of the MR is always challenging because it is rapidly degraded after stimulation and in vitro, but the exact regulation and mechanism requires further investigations. In its unstimulated state, a half-life of 12 h has been described (Faresse et al., 2010). The MR possesses two PEST motifs predicted as candidate ubiquitination sites but mutating them failed to prevent degradation, and therefore, other residues or indirect effects seem to be responsible for rapid MR degradation (Yokota et al., 2004). Unstimulated MR is mono-ubiquitinated, a state stabilized by Tsg101 (Faresse et al., 2012). Removal of mono-ubiquitin followed by polyubiquitination of MR, for example, by CHIP, can be initiated by aldosterone, inhibition of HSP90 or the ubiquitin-specific protease USP2–45, all of which leads to proteasomal degradation and reduction of MR protein levels (Faresse et al., 2010). Conversely, proteasomal inhibition prevents ligand-dependent degradation of MR (Yokota et al., 2004). Protein phosphatase 1a can stabilize MR by inhibiting its interaction with the E3 ubiquitin ligase Mdm2 (Nagarajan et al., 2017).

15 | NON-GENOMIC SIGNALLING

In addition to classical genomic signalling, non-genomic effects have been described for aldosterone that occur within minutes and do not require transcription or translation. At the beginning of aldosterone research, rapid changes in ion fluxes and cardiovascular parameters were reported and these could not be reconciled with genomic effects (Ganong & Mulrow, 1958). Therefore, a novel membrane aldosterone receptor was postulated. Thereafter, it was demonstrated that many non-genomic effects of aldosterone require the presence of classical MR. Cytoplasmic MR can interact with the signalling pathway of different membrane receptors, including receptor tyrosine kinases such as the **EGF receptors** (**EGFR**), **PDGF receptors** (**PDGFR**) and **insulin-like growth factor 1 receptors** (**IGF1R**) and GPCRs, such as **AT_1 receptors** and **GPER1**. Key signalling intermediates are **MAPK**s, **PKC**, **c-Src**, **inositol 1,4,5-trisphosphate** (**IP_3**) and Ca^{++} (Ruhs, Stratz, et al., 2017). Non-genomic MR effects are found in classical MR epithelial target organs or in non-epithelial tissues of pathophysiological relevance, such as heart and vasculature. For example, in the kidney, the activity of key transporters like ENaC, **Na^+,K^+-ATPases** and **NHE** seem to be first non-genomically increased by rapid mechanisms, such as the trafficking of subunits to the membrane, changes in open probability or reduced degradation followed by de novo synthesis of proteins so that non-genomic actions support genomic actions (Ruhs, Stratz, et al., 2017). Likewise, in the cardiovascular system, the MR non-genomically supports vasoconstriction, increases ROS production, enhances contractility, furthers hypertrophy and modulates **NO** availability. Therefore, non-genomic and genomic pathways seem to work mainly in concert to achieve the physiological and pathological MR effects.

16 | SUMMARY AND PERSPECTIVES

Our understanding of the molecular and structural basis for corticosteroid action, including the biology of MR, has steadily advanced in the past few years. This included solving the structure of the DBD and LBD in complex with different ligands, identification of novel PTMs modulating receptor function, extensive work on the molecular basis linking mutations to human disease and dissection of different signalling pathways converging on genomic outcomes. However, many specific aspects of MR biology have been inferred from more extensive work performed on other steroid receptors. Specifically, it is generally assumed that due to the close evolutionary relationship between MR and GR, the two receptors should share most of their molecular and structural characteristics. Accumulating evidence and divergent pathophysiological functions suggest that this may not always be the case. Important questions remain regarding the basic mechanisms providing ligand specificity in gene transcription responses. The importance of heterodimerization with other steroid receptors, particularly with GR, has not been fully addressed. Studying allosteric transitions during receptor activation may open up new strategies for pharmacological modulation of MR. A deeper understanding of chromatin-binding dynamics and interaction with specific co-regulators will also be essential to better understand MR actions. This includes a better characterization of the role of the NTD, which, after all, is the most divergent region with other steroid receptors and most likely to impart most of the specificity to MR action.

16.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org and are permanently archived in the Concise Guide to PHARMACOLOGY 2021/22 (Alexander, Cidlowski et al., 2021; Alexander, Christopoulos et al., 2021; Alexander, Fabbro et al., 2021a, 2021b; Alexander, Kelly et al., 2021a, 2021b).

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

CG: literature search and analysis; writing - original draft preparation; writing - review and editing; preparation of figures. BAP: literature search and analysis; writing - review and editing; preparation of figures. AN: literature search and analysis; writing - review and editing; preparation of figures. DAdlR: literature search and analysis; writing - original draft preparation; writing - review and editing; preparation of figures.

DATA AVAILABILITY STATEMENT

No new data have been generated.

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