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Emerging roles of Atypical Chemokine Receptor 3 (ACKR3) in normal development and physiology

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Abstract

The discovery that atypical chemokine receptors (ACKR***s***) can initiate alternative signaling pathways rather than classical G-protein coupled receptor (GPCR) signaling has changed the paradigm of chemokine receptors and their roles in ***modulating*** chemotactic responses. ***The*** ACKR family has grown ***over the years***, with discovery of ***new*** functions and roles in a variety of pathophysiological conditions. However, the extent to which these receptors regulate normal physiology is still continuously expanding. In particular, atypical chemokine receptor 3 (ACKR3) has proven to be an important receptor in mediating normal biological functions, including cardiac development and migration of cortical neurons. In this review, we illustrate the versatile and intriguing role of ACKR3 in physiology.

Keywords

adrenomedullin; atypical chemokine receptor 3/chemokine receptor 7 (ACKR3/CXCR7); C-X-C motif chemokine ligand 11 (CXCL11); C-X-C motif chemokine ligand 12 (CXCL12); physiology

1. Introduction

1.1 Atypical Chemokine Receptor Family

Originally characterized as decoy or silent chemokine receptors, ***atypical chemokine receptors*** (ACKR) are ***major regulators of*** chemokine internalization, degradation, and transcytosis [1-3]. ***The term "atypical" stems from the observation that ACKRs either lack, or have alterations in the canonical DRYLAIV motif; this motif is found in the second intracellular loop, and is typically required for most G-protein activation and signaling*** [4-9]. Instead, these silent receptors elicit their biological effects through modulation of extracellular ligands, ***and although they do not directly mediate chemotaxis, they participate in chemotactic events through chemokine scavenging and degradation. The family consists*** of five major receptors***:*** ACKR1/DARC, ACKR2/D6, ACKR3/CXCR7,

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ACKR4/CCX-CKR, and ACKR5/CCRL2, and ***includes*** one provisional addition, ACKR6/PITPNM3. Like most chemokine receptors, the ACKRs can also bind to a variety of different ligands to elicit their biological effects. Initially described as regulating innate and adaptive immune responses and leukocyte recruitment, the expansion of ACKR research in recent years has led to alternative roles for ACKRs in physiology, including contributions to cardiovascular and lymphatic vessel growth, embryonic development, and central nervous system function [9-13]. Several recent reviews highlight ***ACKRs concerning*** disease mechanisms, including their roles in cell migration and proliferation [14-18]. Here, we focus our efforts on emphasizing the diverse physiological ligands and roles of ACKR3 beyond participating in chemotaxis (Fig. 1).

1.2 ACKR3 and Ligands

1.2.1 CXCL12 Signaling Mediated by ACKR3—Initially considered an orphan receptor, the discovery that ACKR3 (originally named RDC1 and CXCR7) could bind to C-X-C motif chemokine ligand 12 (CXCL12) challenged the previous notion that CXCL12 ***exerted all of its*** biological functions solely from binding to CXCR4 (Fig. 1) [19]. Interestingly, although ACKR3 possesses the common G-protein coupling DRY motif, it ***binds CXCL12 using*** a unique ***N-terminal*** binding site located ***in extracellular loops two and three*** [20-22]. Although CXCL12 can form homodimers under physiological conditions, ACKR3 preferentially interacts with CXCL12 monomers ***with a*** 10-fold higher affinity compared to CXCR4 [23, 24]. Because this interaction activates β-arrestin recruitment rather than classic $G_{\alpha i}$-protein signaling, one can categorize ACKR3 as a β-arrestin-biased receptor ***that promotes*** CXCL12 internalization and early endosome degradation [6]. The receptor will also undergo ***constitutive*** rapid recycling back to the cell surface, which is necessary for continued membrane localization and activation [25]. Furthermore, recent ***in vivo studies*** have shown that ACKR3 inhibition causes an increase in CXCL12 plasma levels, implicating ACKR3 as an important ***regulator of*** CXCL12 concentration [19, 26-28]. In zebrafish embryos, CXCL12 sequestration by ACKR3 is critical for the primordium to deposit cell clusters across the trunk and tail, facilitating sens ry cues for water flow [29]. Finally, CXCL12 gradient regulation by ACKR3 promotes neural progenitor cell survival [30, 31]. Extensive research focusing on chemotactic properties of ACKR3:CXCL12 interaction has demonstrated successful therapeutic avenues for the treatment of several cancers [32]. However, because previous research primarily focused on the CXCR4:CXCL12 signaling axis, the ***full*** breadth of ACKR3:CXCL12 regulation ***of*** CXCL12 beyond contributing to chemotaxis is still warranted.

ACKR3 ***regulation of*** CXCL12 availability is ***complicated*** further by ***its ability to heterodimerize*** with CXCR4. ACKR3 and CXCR4 co-immunoprecipitate in HEK293 cells and co-localize in Neuro2A cells ***and in*** several tissues [33]. Expression of ACKR3 induces conformational rearrangements within $G_{\alpha i}$ protein complexes of CXCR4, thus impairing $G_{\alpha i}$ protein activation. This modulation ***of*** downstream signaling is partially attributed to ACKR3 β-arrestin signaling. When both CXCR4 and ACKR3 are co-transfected in HEK293 cells there is a concomitant increase in CXCL12-induced β-arrestin co-immunoprecipitation with ACKR3 [33]. Unlike CXCR4 signaling alone, this heterodimeric effect increases ligand-stimulated and membrane recruitment of β-arrestin and causes sustained activation of

ERK1/2 and p38 MAPK signaling pathways [33, 34]. CXCR4:ACKR3 heteromeric complexes have proven to be critical in valve formation in the heart, and integrin activation in T-cells [35-37]. The significance of CXCR4:ACKR3 heterodimers and ***alteration of*** CXCL12 signaling downstream of $G_{\alpha i}$ may be physiologically relevant and remains to be further explored.

1.2.2 ACKR3 is a Low Affinity Receptor for CXCL11—Interestingly, CXCL11 (also known as ITAC) can reduce the heterodimer effects of CXCR4:ACKR3 by modulating β-arrestin recruitment [33]. Treatment with CXCL11 in CXCR4/ACKR3 co-expressed glioblastoma cells ***increased*** cAMP production, leading to the assumption that CXCL11 ***can*** rescue CXCL12 signaling inhibition induced by the CXCR4:ACKR3 heterodimeric complex. However, more research is necessary to ***determine*** how ***exactly*** CXCL11 acts as an allosteric modulator of CXCR4:ACKR3 dimer complexes [33].

Although extensive research has determined the biological implications of ACKR3 on CXCL12 signaling, few studies have focused on ACKR3:CXCL11 pathway ***beyond mediating chemokine scavenging and degradation*** Originally presumed to bind only to CXCR3, CXCL11 also binds to ACKR3 with low affinity. ***For this reason in radioligand binding assays, the affinity of the ^{125}I-CXCL11 tracer is so low that competition assays are performed in a heterologous system with ^{125}I-CXCL12 as the tracer. In this system, CXCL11 inhibits ^{125}I-CXCL12 binding to ACKR3 with an IC50 of 9 nM, whereas CXCL12 inhibits ^{125}I-CXCL12 binding with an IC50 of 1.3 nM*** [38-40]. More recent reports have indicated a 10-fold difference in binding affinity for CXCL11 vs CXCL12, 4 nM and 0.4 nM, respectively [41]. ***As with*** CXCR3, CXCL11 binding to ACKR3 depends on acidic residues of the N-terminus [40]. Not only are high ACKR3 expression levels required for CXCL11 scavenging and degradation, ***but CXCL11 internalizes ACKR3 faster than CXCL12 and delays recycling*** [42] This may be attributed to differences in affinity and dependence on β-arrestin 2 recruitment or ***specific intracellular transport properties for CXCL11*** [26, 40, 42]. Most studies on CXCL11 have primarily focused on inflammatory pathways, due to its characteristics as an inflammatory chemokine, with an increase in activation following interferon stimulation [38]. Research efforts focusing on how CXCL11 modulates ACKR3 will be critical ***for*** determining physiologically relevant disease mechanisms.

1.2.3 Titration of Adrenomedullin by ACKR3—As the closest known paralog to the adrenomedullin receptor (G10D), initial research described ***ACKR3*** as a regulator of the vasodilator peptides, calcitonin gene-related peptide (CGRP) and adrenomedullin (*Adm,* AM) [43]. ***AM binds to*** ACKR3 with high affinity ***(K_d=0.2 nM), similarly to its other receptors, the canonical heterodimeric receptors AM1 and AM_2, suggesting*** the possibility ***that ACKR3 could*** be an additional CGRP and AM receptor [41]. This original breakthrough study led to more research investigating ACKR3 signaling in association with AM. In 1999, Autelitano and Tang determined which AM receptor ***mediated*** AM vasodilation effects by analyzing mRNA expression levels of AM receptors (G10D and CLR) and ACKR3 in lung and vascular smooth muscle cells (VSMC). They determined that expression ***of*** all three receptors ***was*** found in lung, however only ACKR3 was detected in

vascular smooth muscle cells ***(VSMC)*** suggesting ACKR3 as an important modulator in AM VSMC function [44]. Recent studies by Mackay et al. and Klein et al. further confirmed the relationship of ACKR3 with AM. ACKR3 null mice exhibit similar phenotypes as *Adm* knockouts, including lymphatic vascular and heart defects [12, 36]. Additionally, in *Ackr3*$^{-/-}$ mice, semilunar valves of the heart have ***reduced*** *Adm* expression and genes that are consistent with AM function are also suppressed [36]. ***Most importantly, the gain-of-function developmental phenotypes observed in Ackr3*$^{-/-}$ *mice, including cardiac hyperplasia and precocious lymphatic vascular development, can be completely abated by crossing onto a genetic background of AM haploinsufficiceny (Adm*$^{+/-}$ *mice), thereby providing direct genetic and in vivo evidence for ACKR3 as a decoy receptor for titrating the biological effects of AM peptide during embryogenesis*** [12]. Moreover, although there are no changes in survival rates between wildtype and *Ackr3*$^{+/-}$ mice, *Ackr3*$^{+/-}$ mice with genetic *Adm* overexpression exhibit increased lethality ***further illustrating the critical importance of ACKR3 in titrating AM levels***

1.2.4 ACKR3 Facilitates Ligand Concentrations of vCCL2 and adrenal opioid proenkephalin A—Recently, two additional ligands, C-C motif chemokine ligand 2 (vCCL2, also known as vMIP-II) and adrenal opioid proenkephalin A***, have been shown*** to interact with ACKR3. Known as a viral chemokine and encoded by human herpesvirus 8 (HHV-8), vCCL2 is linked to disorders such as Kaposi's sarcoma, primary effusion lymphoma, and multicentric Castleman disease [45, 46]. vCCL2 is a promiscuous ligan d, ***and can bind*** to several chemokine receptors; vCCL2 acts as an antagonist ***for*** CCR1, XCR-1, and CXCR4, and ***acts as*** an agonist for CCR3 and ACKR3 [47, 48]. ***Specifically for ACKR3, the N-loop and cysteine motif of vCCL2 may be important for binding, as truncated vCCL2 peptides (devoid of the N-loop and the cysteine motif) display weaker binding and decreased potency to ACKR3*** [39] In glioblastoma cells transfected with ACKR3, vCCL2 interacts with ACKR3 (IC_{50} of 53.6 + 6.3 nM) but does not trigger cAMP production or typical intracellular calcium mobilization. Instead, vCCL2 acts as an agonist for ACKR3 by recruiting β-arrestin 2 and modifies surface levels of ACKR3 in a concentration-dependent manner. ***As is the case with*** CXCL12, CXCL11, and AM, ACKR3 can perhaps function as a scavenger of vCCL2 by manipulating its concentration and modifying signaling activity [49]. ***Thus, future studies on ACKR3:vCCL2 signaling during viral infection could provide valuable information on host-virus interactions.***

The adrenal opioid proenkephalin A gene encodes peptide precursors for the production and release of opioids into circulation and regulates circadian glucocorticoid oscillation [50]. Intermediate peptides of adrenal opioid proenkephalin A such as BAM22, peptide I, and peptide E can activate ACKR3 through β-arrestin recruitment and increase circadian glucocorticoid oscillation [51]. Specifically, BAM22 is a potent ligand of ACKR3 and when β-arrestin is knocked down in adrenocortical cells, BAM22 signaling ***is*** inhibited. The unexpected discovery that ACKR3 can regulate adrenal opioid proenkephalin A and circadian glucocorticoid oscillation leads to the idea that this receptor could be significant in emotional behavioral outcomes, such as anxiety and depression.

2. Role of ACKR3 in Physiology

2.1 ACKR3 Murine Knockout Phenotypes

More than 95% of ACKR3-deficient mice die by postnatal day 1 with heart development abnormalities including cardiomyocyte hyperplasia and atrial and semilunar valve defects [36, 52]. Several phenotypes for perinatal lethality emerge at embryonic day 18.5 including circulatory failure, atria dilation, and interstitial edema [12, 52]. Of those that do survive to adulthood, most have compromised heart function including severe aortic valve calcification and thickening of aortic leaflets; causing sudden death [52]. ***Furthermore,*** ACKR3 expression in the brain, kidney, and trophoblast cells of the placenta ***suggests*** there may be alternative ***functions for*** ACKR3 in ***addition to cardiac*** physiology [52, 53]. In the next several paragraphs, we will focus on research pertaining to cardiac, neuronal, renal, and reproductive physiology to highlight the exquisite importance of this receptor in ***multiple physiological contexts***.

2.2 Cardiovascular Physiology

Mounting evidence has identified ACKR3 as a key player in cardiac development [12, 35, 36, 52]. As mentioned ***above***, *Ackr3*$^{-/-}$ mice have enlarged hearts ***due to*** cardiomyocyte hyperplasia, and usually die by postnatal day 1 from cardiac valve defects [35, 52]. Moreover, ***vascular*** endothelial cells in the heart, cardiomyocytes, and valve mesenchymal cells express ACKR3 [36, 52, 53]. Although ACKR3 is expressed in cells contributing to heart function and knockouts consequently have heart valve defects, specific regulation of ACKR3 in cardiac function remains to be fully elucidated.

Inhibition of ACKR3 in human umbilical and aorta endothelial cells significantly decreased angiogenesis, suggesting that ACKR3 may be important for vascular function [54]. Conditional endothelial deletion of ACKR3 also impaired heart function and remodeling after myocardial infarction (MI) [54]. In myocardial infarction patients, high circulatory levels of CXCL12 and AM are present, ***which could correlate to the loss of ACKR3*** [54-56]. Indeed, mice with endothelial deletion of ACKR3 and ***experimentally induced myocardial infarction*** have elevated CXCL12 levels ***and*** weakening ***of*** heart function [54]. Conversely, mice that have a genetically engineered 3-fold increase in *Adm* also have ***upregulated*** ACKR3 in cardiac tissue and reciprocal expression patterns for AM and ACKR3 are found in the epicardium and trabeculae. Notably, although *Ackr3*$^{-/-}$ have cardiovascular defects, genetic reduction of *Adm* in these mice (*Ackr3*$^{-/-}$; *Adm*$^{+/-}$) reverses the cardiac hyperplasia of embryos such that they appear ***indistinguishable from wildtype*** [12]. This genetic rescue demonstrates that ACKR3 may be important in alleviating physiological mechanisms related to cardiac failure by regulating CXCL12 and AM signaling. Several reviews have highlighted the critical role of CXCL12 and AM receptors in association with cardiovascular disease; however, ***continued*** ACKR3 research related to these two ligands will be pivotal ***for*** better diagnosing heart complications [57-59].

2.3 Neurobiology

Normal brain function relies on communication between glia cells and neurons, with promising research specifically demonstrating that astrocytes are key controllers of

neurotransmitter homeostasis and synaptic signaling [60, 61]. ***Understanding*** biological mechanisms ***of*** neuronal and astrocyte function ***is important since*** disabled interactions are linked to neurological diseases such as epilepsy, stroke, and hepatic encephalopathy [62]. Several studies have characterized the CXCR4:CXCL12 axis as a significant contributor to neuronal development and central nervous system function [63, 64]. ***Expression of this pair occurs*** in nearly all cell types of the central nervous system and due to its role in neuro-inflammatory response; CXCL12 is linked to ***several*** neurological diseases [65, 66]. Because ACKR3 is an alternative receptor for CXCL12, ***research into their function in the CNS*** will continue to evolve in the field of neurology.

Expression of ACKR3 in neurons and astrocytes has led to interesting discoveries pertaining to ACKR3:CXCL12 signaling in the adult brain [67, 68]. *Ackr3*$^{-/-}$ mutant studies ***have shown that*** ACKR3 is essential ***for*** positioning and regulating migration of cortical neurons. Interestingly, conditional deletion of ACKR3 in interneurons causes insensitivity towards CXCL12 and an increase in CXCL12 concentrations, which can then drive degradation of CXCR4 in the cell [69, 70]. Co-expression of ACKR3 and CXCR4 is observed in migrating medial ganglionic eminence progenitors, and migrating cells in ACKR3-null mice do not produce CXCR4 protein [69]. The relationship between ACKR3 and CXCR4 may therefore be critical for proper neuronal development.

Along with regulating neuronal migration, ACKR3 also modulates CXCL12 signaling in astrocytes and Schwann cells [67, 71, 72]. In rodent and human astrocytes, ACKR3 signals through pertussis toxin sensitive $G_{i/o}$ proteins by binding to CXCL12 and activating Akt and Erk signaling [72]. The role of ACKR3 in neuronal and astrocyte development suggests the importance of ACKR3 in the central nervous system and its potential use as a therapeutic target.

2.4 Renal Physiology

In the kidney, numerous molecular mechanisms help regulate renal blood flow, glomerular filtration rate, and glucose homeostasis [73]. Of these molecular mechanisms, CXCL12, AM, and CXCL11 provide renal protective effects, such as regulating renal vascular development, and glomerular filtration through arteriole expansion [74, 75]. Therefore, ACKR3 may also be critical in renal physiology by altering CXCL12, AM, or CXCL11 concentrations in the kidney. Specifically, podocyte cells support glomerulus function ***by secreting*** CXCL12, and glomerular endothelial cells in close contact with podocytes express CXCR4 [75]. Because interlobular arteries in the kidney also express CXCL12 and CXCR4, and embryos deficient in the ligand or receptor have severe glomerular tuft malformations, paracrine signaling between CXCR4:CXCL12 in glomeruli may be important for proper renal development [75]. Additionally, *Ackr3*$^{-/-}$ embryos have decreased levels of CXCR4 in the nephrogenic zone and glomerular endothelium [76]. ACKR3 localization in renal vesicles and podocytes could therefore be critical for modulating CXCR4/CXCL12 glomerular tuft development.

Most research pertaining to renal function and ACKR3 has focused on the role of ACKR3 in renal carcinoma. In patients diagnosed with renal cancer, ACKR3 expression is increased in renal tumors compared to normal tissue biopsies, with specific localization in blood vessels

[77, 78]. In addition to blood vessel localization in renal carcinoma, ACKR3 expression also increases in blood and lymphatic vessels in human kidneys during allograft rejection [79]. In SCID mice with acute renal failure, neutralization of ACKR3 reduces renal multipotent progenitor cells, which are critical ***for*** improving renal function. Along with being important in the migration of renal multipotent progenitors to sites of renal tissue injury, ACKR3 also regulates their transendothelial migration by promoting adhesion to endothelial cells [80]. Although the importance of ACKR3 in renal carcinoma is evident, more research is needed to elucidate the biological role of ACKR3 in normal kidney function.

2.5 Reproductive Physiology

Much of reproductive research has recognized CXCL12 and AM as important regulators of conception and pregnancy in several species [81-85]. ***As a receptor for these ligands***, it therefore stands to reason that ACKR3 may also play important functions in reproductive physiology.

The ability of CXCL12 signaling to regulate immune cell migration to the uterus, trophoblast invasion, and angiogenic factor synthesis demonstrates its importance at the fetal-maternal interface. Secretion of CXCL12 in trophoblast cells leads to recruitment of peripheral natural killer (NK) cells to the decidua, which along with uterine NK cells, contributes to spiral artery remodeling and fetal immune tolerance [86-88]. Although peripheral NK cells do not express ACKR3, it has yet to be clarified if ACKR3 is expressed in uterine NK cells, and how ACKR3 may regulate this unique population during pregnancy [89]. Along with NK cells, activation of M2 macrophages during pregnancy is also important for embryo survival [90]. Circulating blood monocytes secrete CXCL12 and express CXCR4 and ACKR3; leading to the idea that CXCL12 may function in an autocrine fashion through ACKR3 to regulate monocyte differentiation to specific macrophage populations. Interestingly, inhibition of ACKR3 *in vitro* ***decreases*** M2 macrophage receptor expression on monocytes, implying a potential role for ACKR3 in fine-tuning immune tolerance at the fetal-maternal interface [91, 92]. In addition to possible immune cell regulation, ACKR3 expression is higher in late compared to early term placentas in humans [93]. The reasoning for this expression pattern has yet to be determined, however ACKR3 expression is decreased in trophoblast cells of preeclamptic pregnancies, suggesting ACKR3 expression in late term placentas may be important in the etiology of preeclampsia [94].

AM expression is critical during pregnancy by modifying processes such as uterine receptivity, immune cell recruitment, and spiral artery remodeling [95, 96]. The importance of AM in these processes ***is highlighted*** by observations in animal models. For example, genetic deletion of just one *Adm* allele in female mice leads to a reduction in litter size, abnormal implantation spacing, and diminished pinopode numbers (markers of uterine receptivity). *Adm* also co-localizes with its other receptors during the estrous cycle and they all increase in luminal epithelium prior to blastocyst attachment [97, 98]. ***Like other AM receptors***, ACKR3 expression is increased in uterine tissue during the period of implantation. Thus, it is possible that ACKR3 could contribute to uterine receptivity and embryo attachment through AM [99, 100]. Remarkably, AM plasma levels continually increase throughout pregnancy with highest levels found during the third trimester.

Concurrently, ACKR3 expression also increases in late term placenta, which may contribute to proper AM regulation. While there is still much progress to be made regarding the role of ACKR3 during pregnancy, additional research investigating ACKR3:AM signaling could provide insight into alterations of AM levels in normal and complicated pregnancies.

In addition to regulating female reproductive processes, ACKR3 may also be beneficial in male reproduction. In the testis, spermatogonial stem cells (SSC) are pivotal players in spermatogenesis by sustaining the continuation of spermatogenesis through self-renewal [101]. CXCR4:CXCL12 signaling regulates SSC activities, as disruption of this axis results in SSC loss in vivo and expression of CXCR4 in SSC's, and CXCL12 secretion from Sertoli cells supports SSC self-renewal [102, 103]. Although original studies identified the importance of CXCR4:CXCL12 signaling for the maintenance of spermatogonial stem cells, ACKR3 could also play a role. Recent studies have identified ACKR3 expression in undifferentiated spermatogonia during testicular development, which could mediate spermatogenic repopulation of the seminiferous tubules through regulation of CXCL12 concentrations [104]. It is still unclear the role of ACKR3 in regulating germ cells and other male reproductive processes, but these initial studies demonstrate a potential function of this receptor in supporting testicular development.

Because CXCL12 and AM are critical ligands for healthy reproductive functions, more clarification related to ACKR3 binding to CXCL12 and AM during pregnancy and spermatogenesis is necessary. Identification of pathways that regulate CXCL12 and AM levels will help address novel mechanisms in reproductive physiology, and aid in improving fertility and pregnancy outcomes.

3. Conclusions

Research into ACKR3 signaling continues to flourish and with this comes the daunting task of elucidating new physiologically-relevant functions related to ACKR3 and its five ligands (Table 1). Even as more research unfolds, it is ***becoming apparent that there are still many new*** and exciting avenues for ACKR3 investigation. By better understanding precise mechanisms of atypical chemokine receptor signaling, we can continue to embrace their significance in physiology and their attractive translational research opportunities.

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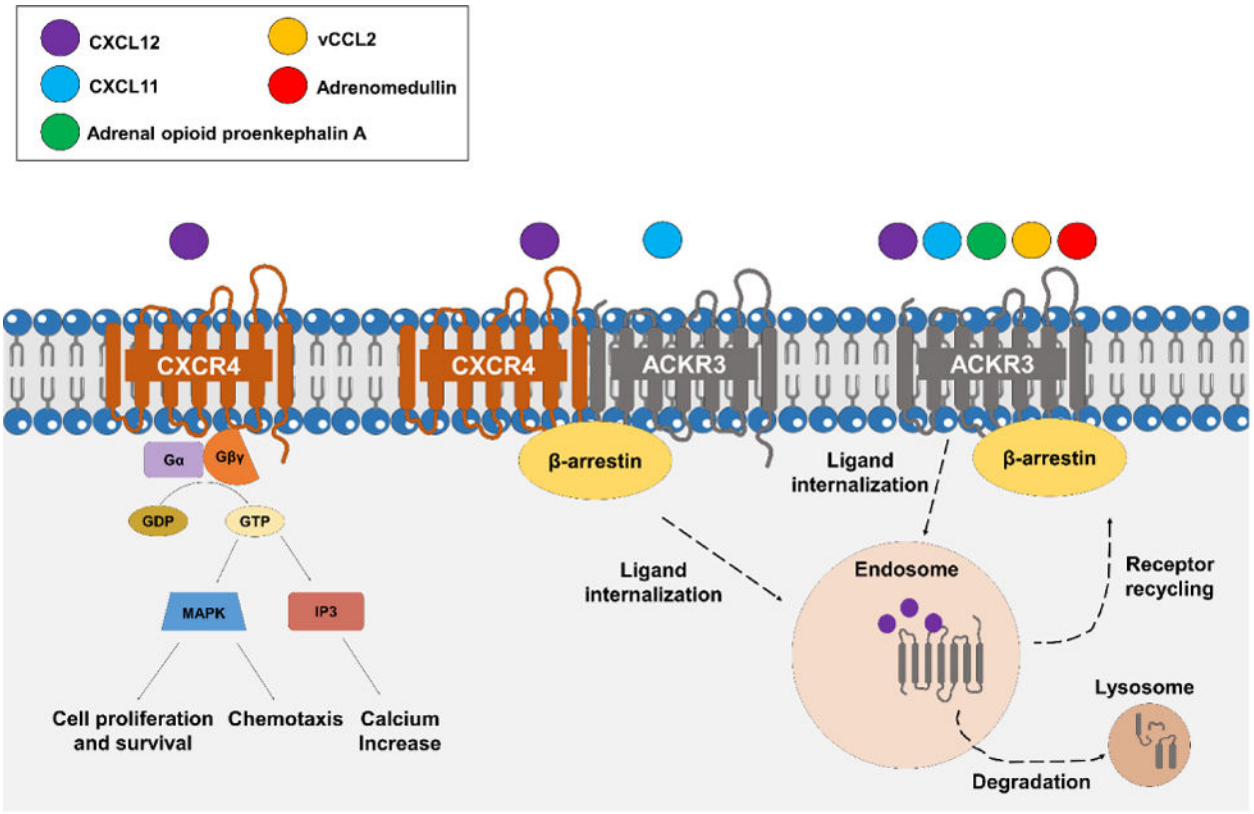

Figure 1.

Distinct signaling pathways for atypical chemokine receptor 3 (ACKR3). Typically, chemokine ligand 12 (CXCL12, purple circle) binds to CXCR4 and activates classical GPCR signaling events such as cell proliferation, chemotaxis and calcium ***influx***. ACKR3 can ***heterodimerize*** with CXCR4, causing conformational rearrangements in G-protein complexes and partiality to β-arrestin rather than classical GPCR signaling ***in response*** to CXCL12 ***binding***. This heterodimer effect is reduced by CXCL11 (blue circle) binding to ACKR3/CXCR4. ACKR3 can also sequester CXCL12, CXCL11, adrenomedullin (red circle), adrenal opioid proenkephalin A (green circle), and vCCL2 (yellow circle) ligands, leading to possible ligand internalization and degradation through β-arrestin recruitment.

Table 1

ACKR3 Ligand Interactions in Physiology [a]

Ligand	Cardiovascular Physiology	Neurobiology	Renal Physiology	Reproductive Physiology	Virology/Immunology
CXCL12 CXCL11	May improve cardiac function by controlling CXCL12 concentrations [56] n.d.	Induces MAPK activation in cortical neurons [70]. Modulates CXCL12 in astrocytes and Schwann cells [67, 71] n.d.	Renal development [75] and carcinoma [77, 78] n.d.	Supports testicular development [104] n.d.	n.d. Inflammatory chemokine [38]
AM	Titrates AM during cardiovascular development [12]	n.d.	n.d.	n.d.	n.d.
vCCL2	n.d.	n.d.	n.d.	n.d.	KSHV [39]
Pro-enkephalin A	n.d.	Circadian glucocorticoid oscillation, behavior [50]	n.d.	n.d.	n.d.

[a] References are provided as brackets in table

[b] not determined, n.d.