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REVIEW
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The G Protein-Coupled Receptor UT of the Neuropeptide Urotensin II Displays Structural and Functional Chemokine Features

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The urotensinergic system was previously considered as being linked to numerous physiopathological states, including atherosclerosis, heart failure, hypertension, pre-eclampsia, diabetes, renal disease, as well as brain vascular lesions. Thus, it turns out that the actions of the urotensin II (UII)/G protein-coupled receptor UT system in animal models are currently not predictive enough in regard to their effects in human clinical trials and that UII analogs, established to target UT, were not as beneficial as expected in pathological situations. Thus, many questions remain regarding the overall signaling profiles of UT leading to complex involvement in cardiovascular and inflammatory responses as well as cancer. We address the potential UT chemotactic structural and functional definition under an evolutionary angle, by the existence of a common conserved structural feature among chemokine receptorsopioïdergic receptors and UT, i.e., a specific proline position in the transmembrane domain-2 TM2 (P2.58) likely responsible for a kink helical structure that would play a key role in chemokine functions. Even if the last decade was devoted to the elucidation of the cardiovascular control by the urotensinergic system, we also attempt here to discuss the role of UII on inflammation and migration, likely providing a peptide chemokine status for UII. Indeed, our recent work established that activation of UT by a gradient concentration of UII recruits Gαi/o and Gα13 couplings in a spatiotemporal way, controlling key signaling events leading to chemotaxis. We think that this new vision of the urotensinergic system should help considering UT as a chemotactic therapeutic target in pathological situations involving cell chemoattraction.

Keywords: G protein-coupled receptor, UT, urotensin II, proline, chemokine, migration

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INTRODUCTION

The urotensinergic system was previously considered as being linked to numerous pathophysiological states, including atherosclerosis, heart failure, hypertension, pre-eclampsia, diabetes, renal disease, as well as brain vascular lesions. Based on this expectation, validation of urotensin II (UII) receptor (UT) antagonism in cell lines expressing rat or human UT, observations in animal models, and even clinical results were not as beneficial as expected, probably because of the complex effects of the urotensinergic system depending on the vascular bed, the studied animal species, and/or

the administration route. Thus, it turns out that the actions of the UII/UT system in animal models are currently not predictive enough in regard to their effects in human clinical trials, thus many questions remain regarding the overall signaling profiles of UT leading to complex involvement in cardiovascular, inflammatory responses, and cancer. We, here, propose that UII may rather play chemokine functions leading to long-term tissue remodeling and tumorigenesis, at least in part due to the pleiotropic functions of UT oriented toward chemoattractant activities.

THE UII PEPTIDE SYSTEM

Endogenous Urotensinergic Peptide Ligands, from Gene to Sequence

At the end of the 1960s, Drs. Bern and Lederis attributed the name "urotensins" to a series of biologically active peptides isolated from the urophysis neurosecretory system of the teleost fish *Gillichthys mirabilis*. Among those, UII was characterized through its ability to stimulate smooth muscle cells (1). Then, the amino acid sequence of UII was subsequently identified in a number of other fish species, and the presence of the UII peptide was discovered in the brain of a tetrapod, the frog *Rana ridibunda* (2, 3) two decades later (**Table 1**). Based on these observations, the gene encoding UII has been the subject of more research and was successfully identified in various mammalian species including in monkey and human (**Table 1**) (4, 5). The neuropeptide UII is composed of 11 amino acids in primates (including *Homo sapiens*) to 17 amino acids in the mouse and shows remarkable conservation of the C-terminal CFWKYC hexapeptide portion formed by the covalent disulfide bridge (**Table 1**) during evolution, suggesting a crucial importance of the cycle in biological activity. To date, UII has been characterized in a single species of invertebrates, the *Aplysia californica* (6), in a form composed of 20 amino acids and whose cyclic hexapeptide differs from vertebrates by only two residues (F→L and Y→V) (7).

All the amino acid sequences of UII identified so far are mostly deduced from cDNAs and correspond to the C-terminal part of its precursor. In human, the deduced sequence of prepro-UII, cloned from colon tumor or placental library, evolved from alternative splicing of the human UTS2 gene, yielding a 124 (isoform b, NP_006777) and 139 (isoform a, NP_068835.1) amino acid variants. The two encoded isoforms are identical for the last 97 amino acids but differ at their N-terminal end exhibiting the signal peptide. The mature peptide UII results from the proteolysis of preproprotein UII at the tribasic site KKR by a specific urotensin converting enzyme (UCE), which is not still identified (4, 5). Study on the conversion of a 25 amino acid C-terminal fragment of preproprotein to mature peptide revealed that the endoprotease Furin and the serine protease trypsin, may act, respectively, as intracellular and extracellular UCE (12). This enzymatic cleavage appears necessary to confer biological activity (13).

In comparison with primate prepro-UII, precursors of rat and mouse UII markedly diverge by the amino acid composition of the N-flanking domain of the cyclic hexapeptide and by the absence of a typical cleavage site (KKR) for pro-hormone converting enzymes in the upstream region of UII sequence (10). These observations led Sugo and collaborators to characterize UII immunoreactivity detected in the brain of the two rodent species and to isolate, in 2003, a peptide similar to UII, the

TABLE 1 | Comparison of the sequences of urotensin II (UII) and urotensin II-related peptide (URP) in different species of tetrapods.

Family	Species		Peptide sequences	
	Scientific names	**Common names**	**UII**	**URP**
Tetrapods	*Pelophylax ridibundus*	Frog	AGNLSECFWKYCV(2)	
	Hyla arborea	Tree frog	AGNLSECFWKYCV(2)	
	Xenopus laevis	Xenope	GNLSECFWKYCV	ACFWKYCV
	Gallus gallus	Chicken	GNLSECFWKYCV	ACFWKYCI
	Taeniopygia guttata	Zebra finch	GNLSECFWKYCV	ACFWKYCI
	Felis catus	Cat	GSPSECFWKYCV	
	Sus scrofa	Pig	GPPSECFWKYCV (8)	
	Ovis aries	Sheep	GPSSECFWKYCV	
	Bos taurus	Cattle	GPSSECFWKYCV	ACFWKYCV
	Rattus norvegicus	Rat	QHGTAPECFWKYCI (5)	ACFWKYCV (9)
	Mus musculus	Mouse	QHKQHGAAPECFWKYCI (10)	ACFWKYCV (9)
	Otolemur garmettii	Galago	GTPSECFWKYCV	ACFWKYCV
	Callithrix jacchus	Marmoset	ETPDCFWKYCV	
	Papio anubis	Baboon	ETPDCFWKYCV	ACFWKYCV
	Macaca mulatta	Rhesus monkey	ETPDCFWKYCV	ACFWKYCV
	Macaca fascicularis	Macaque	ETPDCFWKYCV	
	Nomascus leucogenys	Gibbon	ETPDCFWKYCV	
	Pongo abelii	Orangutan	ETPDCFWKYCV	ACFWKYCV
	Gorilla gorilla	Gorilla	ETPDCFWKYCV	ACFWKYCV
	Homo sapiens	Human	ETPDCFWKYCV (5)	ACFWKYCV
	Pan paniscus	Bonobo	ETPDCFWKYCV	ACFWKYCV
	Pan troglodytes	Chimpanzee	ETPDCFWKYCV (11)	ACFWKYCV

The biologically active sequence of the peptides, highlighted in red, is conserved in all tetrapods.

urotensin II-related peptide (URP) (9). Later on, the cloning of the prepro-URP cDNAs, in human, mouse, and rat revealed 54% homology between human and rat vs 47% homology between human and mouse (14). However, the URP sequence is identical in all mammals and corresponds to human Ala^{1}–$UII_{4–11}$. Finally, although URP was initially thought to exist only in tetrapods, its gene has been identified in the genome of several teleost fishes (15, 16). Together, the sequences of UII, URP, and somastostatin display high homology in particular at the level of the cyclic hexapeptide sequence and it was established that URP is a peptide paralog of UII (17).

General Distribution of UII and Urotensin II-Related Peptide

Urotensin II and URP are widely distributed in the cardiovascular, renal, and endocrine systems. In humans, high expression levels of UII are found in the myocardium (18), the atria, and the ventricles (19–21). UII has also been detected in the heart of rats (4, 9, 20) and mice (11, 22). At the vascular level, the presence of mRNA for prepro-UII has been demonstrated in the arterial network, primarily in the thoracic aorta, pulmonary arteries, and arterioles. In contrast, it is almost absent in the venous network, with the exception of the saphenous and umbilical veins (19–21).

Several studies show that kidney is a major site of production of circulating UII in humans (9, 20, 21, 23, 24). The peptide is particularly abundant in glomerular epithelial cells, convoluted tubules, and collecting ducts (20, 25). Surprisingly, the level of expression of UII in the kidney of monkey and mice is weak (11), stressing some important differences between species. UII is also expressed in endocrine glands, such as pancreas or adrenal gland, in humans and rats (5, 23, 26). Nevertheless, the mRNA for UII is undetectable in these tissues in monkey and mice (11, 22), again raising the question of the occurrence of a conserved cardiovascular and/or endocrine role of UII among the different species.

Even though the identification of URP has been done more than 10 years ago, data concerning this peptide are considerably much more incomplete. Nevertheless, it is worth noting that the expression of prepro-URP is predominant in the gonads and placenta of humans and in the testis of rats (9). URP and its mRNA are also expressed in kidney (8, 9) and in the ventricles and myocardium of the rat heart (27, 28). The expression of the two peptides extends to the spleen, thymus, liver, stomach, and intestines (5, 9, 11, 20, 22, 23, 29, 30).

Within the central nervous system (CNS), UII immunoreactivity is mainly associated with motoneurons of the hypoglossal nucleus of the brainstem and the ventral horn of the spinal cord. This neuronal subpopulation also strongly expresses UII in the nuclei of the abducens, facial, trigeminal, and hypoglossal cranial nerves in rats (10, 31) and those of the caudal part of the spinal cord in mice (10, 32), rats (10, 31), and humans (4, 5). Surprisingly, UII is apparently absent from the brainstem of monkey (4, 11). URP mRNAs are localized in the spinal cord of humans and rats, at expression levels considerably lower than those of UII (9). In mice, URP mRNA is found in the brainstem and in motoneurons of the anterior horn of the spinal cord (22). Finally, URP is present in neuronal cell bodies of the preoptic region and in fibers of the median eminence and the organum vasculosum of the lamina terminalis, which is involved in thermoregulation (33).

Thus, UII and URP are not ubiquitously expressed within the peripheral and central nervous systems and likely show key expression levels in heart, arterial networks, and kidney with discrepancies between species, suggesting a non-conserved role in the vasomotor tone regulation.

UII RECEPTOR UT RECONSIDERED IN LIGHT OF CONSERVED STRUCTURAL PROPERTIES

The UT receptor was initially discovered and cloned in 1995 from rat sensory tissue extracts (34) and a rat genomic library (35). At this stage, this G protein-coupled receptor (GPCR) was named sensory epithelium neuropeptide-like by Tal et al. (34) and GPR14 (according to the current nomenclature) by Marchese et al. (35). Whereas Ames et al. identified the UII peptide as the endogenous ligand of the human receptor homologous to GPR14 by reverse pharmacology (4), other research teams in the same year corroborate the existence of the UII/GPR14 system in various species (8, 36, 37). It is on the basis of these studies that the receptor was renamed UII receptor or UT, by the International Union of Basic and Clinical Pharmacology (IUPHAR).

Distribution of UT Varies Depending on Species and Systems

The presence of substantial amounts of UII in the cardiovascular system has led several groups to investigate the expression of UT mRNA in different component tissues in rat (37–39) and mouse (36). In human and monkey, high levels of mRNA-encoding UT have been detected in the myocardium (18), the atria (4, 11, 21, 23), and the ventricles (4, 20, 23). At the vascular level, the presence of UT has been detected in the thoracic aorta (4, 21, 40) as well in the pulmonary and coronary arteries (41). In addition, UT, like UII, is strongly expressed in kidney from rat (27, 38, 42–46) and human (21, 23, 24, 41, 47), although it is only moderately expressed in monkey (44). UT is also present in the endocrine system, notably in the pituitary, pancreas, and adrenal gland in human (4, 23), monkey, and mice (11). Other peripheral tissues show significant levels of UT expression, which varies according to the species studied. The CNS shows widespread expression of UT mRNA, which is particularly abundant in the brainstem and spinal cord (23, 24, 36, 38, 48).

Other regions of the CNS, e.g., the cortex, hypothalamus, and thalamus, display relatively weak expression levels that vary between species. UT is also associated with cerebral blood vessels and is expressed mainly in the endothelial cells of microvessels (49). Finally, the expression of the receptor has been detected both in neurons (48) and in a subpopulation of astrocytes in the brainstem and hypothalamus (50) and in cultured cortical astrocytes (51).

Together, this UT distribution highly resembles the UII/URP distribution in cardiovascular endocrine and also nervous tissues, naturally leading several groups to investigate the effects of UT on the cardiovascular system, even if the data remain

multiple and complex. In human, circulating levels of UII and/or URP ("UII-like") are higher in patients with heart failure (52, 53), systemic (54) or portal hypertension (55, 56), or atherosclerosis (57), than in plasma of healthy volunteers. In fact, the UT-related mechanisms appear associated with tissue remodeling processes during the course of the disease (58), including cardiac hypertrophy and fibrosis (59). Thus, we here question whether UT may play an alternative chemokine-like function in primates than vasomotor regulatory activities as previously proposed in rats.

The UT Positioning Depends on the Different GPCR Classifications

Although GPCRs share a common structure, certain characteristics make it possible to distinguish and to classify them in different families. However, based on the homology of sequence, structure, ligand binding mode, or phylogenetic relationships, the large number of GPCRs makes it difficult to develop a global classification system. The human UT receptor was shown to belong to the class A (Rhodopsin) GPCR family (60) according to the widely used structural classification in the past, based on the identification, by analysis of protein sequences of the TMs of the GPCRs listed in vertebrates and invertebrates, of fingerprints preserved within certain GPCR groups (61). GPCR members of class A (the largest family of GPCRs with 80% of GPCRs listed) share homologies of sequence, structure, and ligand-binding mode. The homologies of sequence between the receptors of class A can be very low since they rely on the conservation of a few residues mainly located in the TMs, which would play a primordial role in their structure and functionality. Within this classification, UT displays sequence homology not only with certain somatostatin receptors (SST), in particular with SST4 (27%), but also opioïdergic receptors (MOR: 26%, DOR: 26%, and KOR: 25%) (35), which are now crystallized (62, 63) and would constitute the best prototypes for UT modeling.

More recently, Fredriksson et al. (64) proposed from the GPCR sequences a yet commonly used systematic classification system named GRAFS formed by the five distinct families of *Glutamate* (G), *Rhodopsin-like* (R), *Adhesion* (A), *Frizzled/Taste* (F), and *Secretin* (S). The Rhodopsin-like family showed a clear evolutionary success since containing around 90% of the GPCRs and is divided into four (α, β, γ, and δ) subclasses in Fredriksson's classification. The crystallographic structures of Rhodopsin-like family indicate a common firm core corresponding to high conserved sequence motifs, i.e., E/DRY in TM3, NPXXY on TM7, WXP on TM6, D2.50 in TM2 (*X*.50, according to the Ballesteros classification: *X*, numbering of TM; 50, the most conserved residue in the concerned TM) (65), and a water network that can be seen in the binding pocket mediating ligand interactions with the receptor (66). It can be noticed that the γ group includes 59 GPCRs, divided into three different clusters, i.e., SOG (15 GPCRs like SST, OR or GPR54 receptor also named KISS1R), melanin-concentrating hormone receptors (MCHR) (2 GPCRs), and CHEM (42 GPCRs) including chemokine receptors, such as the CXCR4, angiotensin (ANG), and bradykinin (BK) receptors, as well as a large number of orphan receptors. However, the neighbor-joining and maximum parsimony method used in sequence analysis failed to affect 23 receptors into one family/group/cluster, and this is the case for UT (named GPR14 in this study). These difficulties were due to an unusual part of the GPCR gene sequence in question [usually coding for intra- (i) or extracellular (e) loops] that would result from a chimeric origin of the receptor and/or progressive pressure not shared by neighboring receptors (64). However, UT shares the sequence pattern characteristic of Rhodopsin-like GPCRs. When comparing different sub-families of GPCRs from the conserved ligand binding pocket or from conserved endogenous agonist ligands (67), UT can be found near GPR109A or purinergic P2Y receptors listed in orphan receptors from the SOG or PUR cluster group by Fredriksson et al. (64, 67). In light of these results, we suggest that UT possesses specific structures and functions related to the chemokine receptors of the SOG and PUR families.

Thus, as members of the Rhodopsin SOG and PUR family, UT has a relatively short N-terminal domain with two N-glycosylation sites (N29 and N33), a NLxxxD2.50 motif within its TM2, a disulfide bridge between cysteine residues in the extracellular end of TM3 and the e2 loop, a ER3.50Y motif at the cytoplasmic end of the TM3, a CFxP6.50 motif within the TM6, the highly conserved NP7.50xxY motif at the TM7 level, and a palmitoylation site at the C-terminal tail (C334) (68). Other specific motifs are observed, namely (i) a KRARR nuclear localization motif at the i3 loop (69), (ii) potential sites of phosphorylation by protein kinases A and C, kinase I, and glycogen synthase kinase 3 at i2 and i3 loops (35, 68, 70), (iii) serine potential phosphorylation sites at the C-terminal end involved in β-arrestin interaction and internalization of the receptor (71, 72), and (iv) polyproline type I and II motifs within the C-terminal tail potentially allowing the interaction with proteins harboring src homology 3 type domains (**Figure 1**).

UT Shares a Structural Feature with Chemotactic GPCRs: An Evolutionary Lighting

These human GPCR classifications were proposed from constructions of phylogenetic trees, which require the use of several methods to assess the robustness of the obtained results. However, other strategies should be used when a position dependency hypothesis is questioned, the size of the dataset becomes large, and/or the relationships between proteins of the same family but of different genomes must be compared. Thus, to address some ambiguities concerning GPCRs classification, as highlighted for UT, analyses of gene sequences by the metric multidimensional scaling (MDS) were conducted. MDS is also called "principal coordinates analysis" and corresponds to an exploratory multivariate procedure designed to identify patterns, within proteins for example, in a distance matrix (73, 74). With MDS, protein sequences can be considered all at once, and individually represented in a low-dimensional space whose respective distances best approximate the original distances. In addition, MDS allows the projection of supplementary information allowing a straightforward comparison of the active and supplementary data. Therefore, MDS was used to explore the sequence space of GPCR families and to interpret patterns in relation with evolution, with projection of GPCR

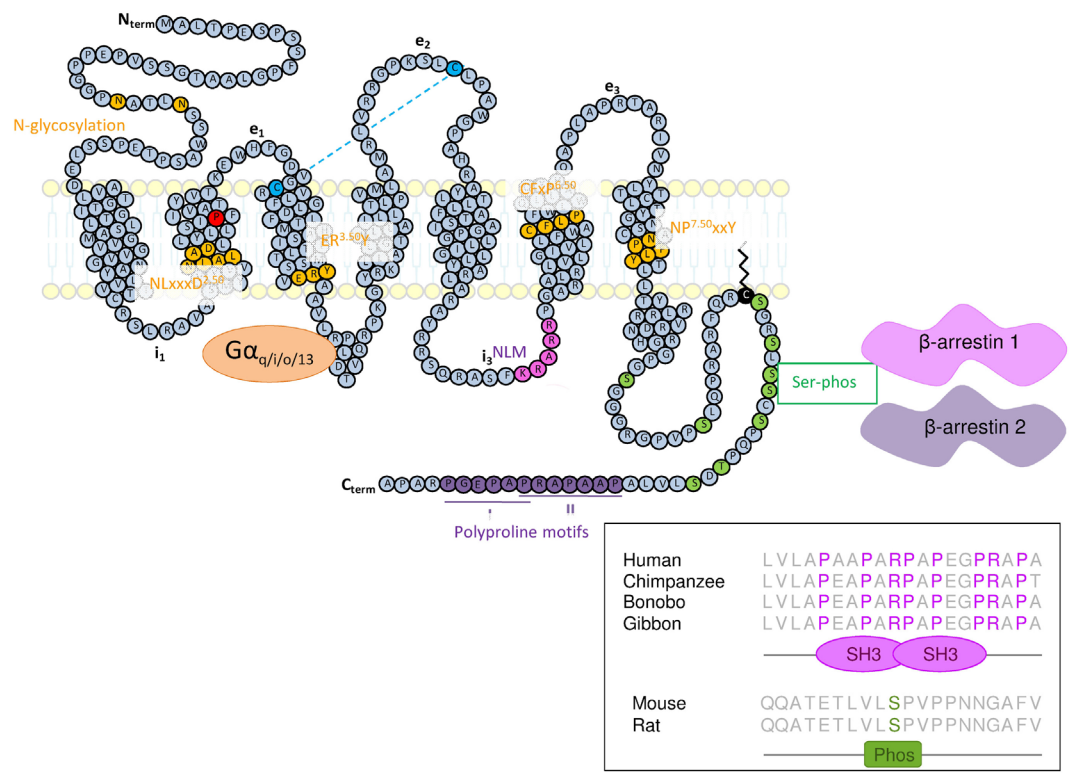

FIGURE 1 | Schematic representation of the structure of human UT. The amino acids represented in yellow represent highly conserved residues within class A/Rhodopsin G protein-coupled receptor of which the UT is belonging. It concerns two N-glycosylation sites in the N-terminal part (Nterm), a NLxxxD motif in TM2, a ERY motif at the cytoplasmic end of the TM3, the CFxP motif in TM6, and NPxxY within the TM7. The key proline in position 2.58 appears in red within the TM2. The two cysteine residues involved in the disulfide bridge between the extracellular end of the TM3 and the e2 loop appear in blue. A nuclear localization motif (NLM) sequence (in pink) was also identified in i3 loop. In addition to these consensus motifs, the C-terminal tail of UT exhibits Serine phosphorylation sites (in green) potentially involved in β-arrestin 1 and 2 anchoring, cysteine, palmitoylation site and plasma membrane anchor (black) sites, as well as two polyproline type I and II motifs (in violet) extracted from analysis by Scansite (http://scansite3.mit.edu#home). Inset, the alignment of the UT C-terminal (C-term) sequence shows that the prolyproline motif allowing interaction with SH3 protein domain, is specifically conserved in hominoids.

sequences from distant species onto the active space of human GPCRs (75, 76), based on the assumption that GPCR evolution could follow a radial rather than bifurcated path (represented by the classical phylogenetic tree system). The phylogenetic links between GPCRs of the same species were represented in three dimensions, and the results were shown superimposed between several species (75). By means of this evolutionary-based classification, the work of the Chabbert's group succeeded in identifying GPCRs of the Rhodopsin class in the same clusters as those found by Fredriksson et al. (76), but some differences at the margin were also identified and likely stressed the way how some GPCRs may be activated and function. The differences are as follows: galanin receptors and Kiss1R belonging to the SOG cluster in the Fredriksson et al. classification, are likely rather connected to the PEP cluster according to Chabbert et al., and then SOG becomes SO cluster. In addition, the MCHR and UT appeared in this new classification, grouped in this SO cluster (76).

This is probably the evolutionary point of view that gives the best indications about UT membership and structural characteristics. Indeed, MDS analysis of GPCRs of the Rhodopsin family allowed the receptors to be sorted into four groups (G0–G3) comprising different clusters (76). The group G0 represents the central group and includes the clusters PEP, OPN, and MRN, the group G1 includes the cluster SO (SST, OR, and UT), CHEM, and PUR (**Table 2**), the group G2 contained AMIN and AD clusters and finally G3 involves LGR, MEC, PTG, and MRG clusters (**Table 2**). It is interesting to note that in *C. intestinalis*, the CHEM cluster only slightly differs from the SO cluster, thus suggesting that this SO/CHEM group gave rise, in vertebrates, to SO, CHEM, and PUR clusters, suggesting a common origin. Moreover, the cluster SO and PEP are close in the most distant ancestral species from human and their distance increases during evolution (75). These observations argue in favor of a common origin between PEP and SO, CHEM, and PUR clusters (76) and allow the repositioning of UT from a "peptide family (PEP)" group to a chemokine receptor family.

Sequence comparison of the different groups (G0–G3) shows that the main characteristic of the G1 group receptors, including UT is a proline within the TM2 in position 2.58 (P2.58), often preceded by an aliphatic residue whereas G0 group mainly comprises

TABLE 2 | Assignment of the 13 non-olfactory human G protein-coupled receptor clusters from the rhodopsin class into four groups, G0, G1, G2, and G3, in addition to an UC.

Group	Family	Pattern	*Homo sapiens*
G0	PEP *Peptide*	P2.58	MTLR, GHSR
		P2.59	NMUR1, NMUR2, NTR1, NTR2, GPR39, EDNRA, EDNRB, ETBR2, GPR37, PKR1, PKR2, NPY1R, NPY2R, NPY4R, NPY5R, BRS3, GRPR, NMBR, CCKAR, GASR, QRFPR, OX1R, OX2R, NPFF1, NPFF2, PRLHR, GNRR2, GNRHR, GPR83, GALR1, GALR2, GALR3, KISSR, GP151, GP173, GPR19, GPR27, GPR84, GPR85
		P2.60	V1AR, V1BR, V2R, OXYR, TRFR
		NoP	NK1R, NK2R, NK3R, GP150
	OPN *Opsin*	P2.59	OPN4, OPSX
		P2.60	OPSB
		NoP	OPN3, OPN5, RGR, OPSR, OPSD
	MTN *Melatonin*	P2.59	MTR1A, MTR1B, MTR1L
G1	**SO** *Somatostatinergic opioïdergic*	**P2.58**	OPRM, OPRD, OPRK, OPRX, SSR1, SSR2, SSR3, SSR4, SSR5, NPBW1, NPBW2, **UT**, MCHR1, MCHR2
	CHEM *Chemokine*	**P2.58**	CCR5, CCR2, CCR3, CCR1, CCR4, CCR8, CX3C1, CCRL2, CCBP2, XCR1, CCR9, CCR7, CCR6, CCRL1, CXCR4, CXCR2, CXCR1, CXCR5, CCR10, CXCR3, CXCR6, CXCR7, RL3R1, RL3R2, ADMR, AGTR1, AGTR2, BKRB1, BKRB2, APJ, GPR25, GPR15, C5ARL, C5AR, C3AR, GPR44, FPRL1, FPRL2, FPR1, LT4R1, LT4R2, CML1, GPR32, GPR33, GPR1
		NoP	GP152
	PUR *Purinergic*	**P2.58**	P2RY1, P2RY2, P2RY4, P2RY5, P2RY6, P2RY8, P2RY9, P2Y10, P2Y12, P2Y13, P2Y14, PTAFR, SUCR1, OXER1, OXGR1, G109A, PSYR, SPR1, CLTR1, CLTR2, PAR1, PAR2, PAR3, EBI2, FFAR1, FFAR2, FFAR3, GPR4, GPR17, GPR18, GPR20, GPR31, GPR34, GPR35, GPR55, GPR81, GPR87, GPR92, GP132, GP141, GP174, GP171, Q5KU21, GPR82
		P2.58P2.59	P2Y11, PAR4
G2	AMIN *Aminergic*	P2.59	5HT1B, 5HT1D, 5HT1E, 5HT1F, 5HT1A, 5HT7R, 5HT4R, 5HT2A, 5HT2C, 5HT2B, 5HT5A, HRH1, HRH2, HRH3, HRH4, DRD1, DRD2, DRD3, DRD4, DRD5, ADA1A, ADA1B, ADA1D, ADA2A, ADA2B, ADA2C, ADRB1, ADRB2, TAAR1, TAAR2, TAAR3, TAAR5, TAAR6, TAAR9
		P2.59P2.60	5HT6R, ADRB3
		NoP	TAAR8, ACM1, ACM2, ACM3, ACM4, ACM5
	AD *Adrenergic*	P2.59	AA2AR, AA2BR, AA1R, AA3R
G3	LGR *Glycoproteins*	NoP	LGR4, LGR5, LGR6, RXFP1, RXFP2, TSHR, LSHR, FSHR
	MEC *Melanocortin Cannabinoid*	NoP	ACTHR, MSHR, MC3R, MC4R, MC5R, CNR1, CNR2, EDG1, EDG2, EDG3, EDG4, EDG5, EDG6, EDG7, EDG8, GPR3, GPR6, GPR12
	PTGR *Prostaglandin*	P2.59	PE2R2, PE2R3, PE2R4, PD2R, PI2R
		NoP	TA2R, PF2R, PE2R1
	MRG *Mas-related*	NoP	MAS, MAS1L, MRGRF, MRGX1, MRGX2, MRGX3, MRGX4, MRGRD, MRGRE
UC	UC	P2.58	GPBAR, GP120, Q5KU14, GP146
		P2.59	GPR22, GPR26, GPR45, GPR61, GPR62, GPR63, GPR75, GPR78, GPR88, GP101, GP135, GP161, GP176
		P2.60	GPR21, GPR52

Abbreviations of the SO, CHEM, and PUR clusters of the G1 group displaying a P2.58 are in bold. The SO family containing UT is shown in red. The receptors with their most common abbreviations belonging to each of the clusters in the G0–4 and unclassified group (UC) groups are listed [from Pelé et al. (76)].

receptors harboring a proline in position 2.59. Together, only the G1 group, which includes the SO containing UT, CHEM, and PUR clusters, is therefore characterized by a proline P2.58 (75, 76) (**Figure 2A**). Given the phylogenetic links between the PEP, SO, CHEM, and PUR clusters, it is proposed that the position of the proline in 2.58 for the SO, CHEM, and PUR clusters results from a codon deletion in the TM2 of receptors of the PEP family. This proline in TM2 either on P2.58 or P2.59 induces a typical elbow observable by modeling (77, 78) and confirmed by crystallographic studies (79–81), yielding bulge and kink structures, in P2.59 and P2.58 receptors, respectively (**Figures 2A,B**). In fact, by plotting the curvature and flexibility of the TM2, the position

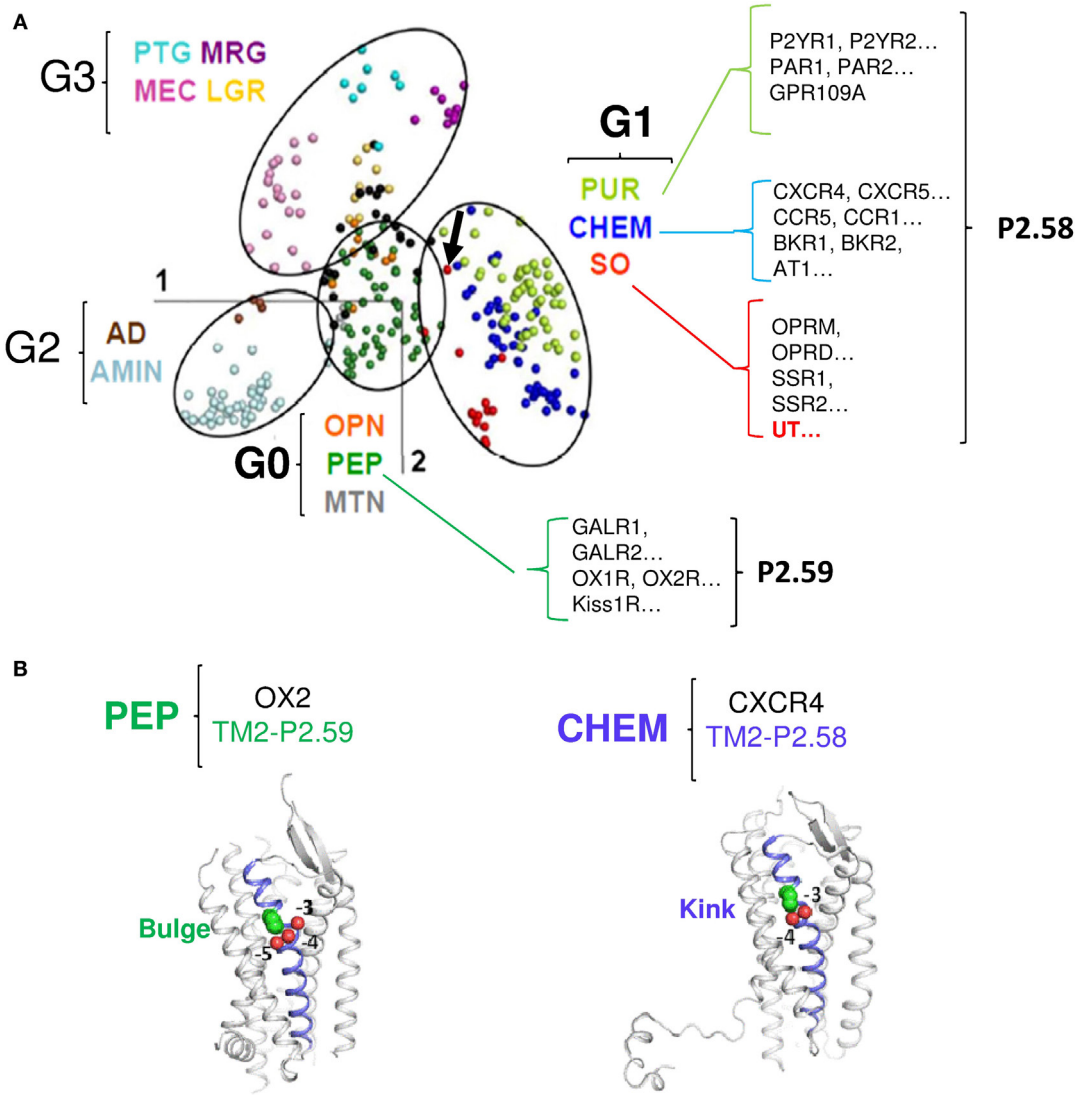

FIGURE 2 | Classification of the different G protein-coupled receptor (GPCR) sub-families according to the multidimensional scaling (MDS) analysis and focus on the proline position in TM2 of receptors from the G0 and G1 groups. (A) In the MDS representation of Rhodopsin-like GPCRs, receptors are visualized as points, with the distances between points as close as possible to the distance in the identity matrix [from Ref. (76)]. The points cluster into four groups, highlighted by ellipses. The color code indicates receptor sub-families and is given in the Figure along with the group the sub-family belongs to. Examples of receptors with the position of the TM2 proline are shown for the G0 and G1 groups. The arrow indicates the position of UT [modified from Ref. (76)]. **(B)** Cartoon view of the PEP receptor OX2 (P2.59, PDB access number: 4S0V, *left panel*) and of the CHEM receptor CXCR4 (P2.58, PDB access number: 3ODU, *right panel*). TM2 is slate. The TM2 proline (green) and the preceding oxygen (red) are shown as spheres. In CXCR4, P2.58 is close to the carbonyl groups at positions −3 and −4 (proline kink). In OX2, P2.59 is close to the carbonyl groups at positions −4 and −5 (proline bulge). Thus, according to the position 2.58 or 2.59 of the TM2 proline, the structure of TM2 presents a kink or a bulge.

of the proline could affect the degree of opening of the GPCR-binding pocket and their activation mechanisms (82). Thus, the change in conformation of the TM2, following the deletion of a residue within the TM2 helix, would contribute to the emergence of activation mechanisms specific to SO, CHEM, and PUR cluster receptors.

As many CHEM and PUR receptors are widely recognized as mediating chemotaxis and chemoattractant behaviors, we propose that the P2.58 and kink feature the TM2 of UT, has allowed the capacity of UII gradient sensitivity and chemotactic behavior, leading to cell migration and invasion.

UII/UT SYSTEM, FROM CARDIOVASCULAR FUNCTIONS TO CHEMOKINE PROPERTIES

Physiological and Pathophysiological Effects of the Urotensinergic System on the Cardiovascular Functions

The distribution of UT and its endogenous ligands has naturally led several groups to investigate the effects of UT on the cardiovascular system. When applied to de-endothelialized aortic rings from

rats (4, 36, 83, 84), rabbits (85), macaques (4), or humans (20, 41, 42, 86–88), UII induces dose-dependent constriction. This effect is observed at doses so low that this neuropeptide was considered the most potent naturally occurring vasoactive compound (4, 20). For example, in a murine model, UII is 660 and 16 times as powerful as serotonin and endothelin, respectively (4). This vasoconstrictive activity is primarily relayed by the mobilization of cytosolic calcium (4, 36). Calcium recruited by UT is derived partly from an intracellular pool *via* the activation of channel receptors sensitive to inositol triphosphate (IP_3) and partly from the extracellular pool *via* L-type calcium channels (89–92). Calcium activates calmodulin, whose blockade inhibits the effects of UII on the contraction of rat aortic rings (89). Calmodulin in turn activates myosine light-chain kinase, responsible for the phosphorylation of MLC-2 and the contraction of actomyosin (93, 94). In the sidelines of this principal intracellular signaling pathway, other pathways involved in the contractile activity of UII, such as the PKC/ERK and the RhoA/ROCK pathways, have also been identified (92–95).

However, when injected as an intravenous bolus in anesthetized or conscious rats, UII and URP provoke a slow and prolonged decrease in arterial pressure due to vasodilatation (9, 96–98). In contrast, chronic administration of UII to these animals has no effect (99). In primates, intravenous administration of UII exerts a strong vasodilatation, responsible for cardiovascular collapse and cardiac arrest at high doses (4, 100). However, results in humans are more controversial, since the intravenous injection of UII leads to local vasoconstriction (101) or has no apparent effect (102–104). Studies investigating skin microcirculation even showed that UII infusion through iontophoresis induces a dose-dependent vasodilatation in healthy volunteers but a dose-dependent vasoconstriction in patients with chronic heart failure, systemic hypertension, cirrhosis, or diabetes without cardiovascular pathology (54, 105–107). Finally, endothelium alterations observed in these pathologies could alter vasodilator properties of UII and explain, at least in part, the differences between patients and healthy volunteers.

Overexpression of UII, URP, and UT in the heart of rats and humans with heart failure has also been demonstrated (13, 28) with a correlation between UII plasma level and the cardiac dysfunction (108). A strong "UII-like" immunoreactivity was seen in coronary artery endothelial cells from patients with atherosclerosis (20, 109), associated with a significant effect of UII on the proliferation of vascular smooth muscle cells (95, 110) or the formation of foam cells (111, 112). Moreover, in rat models, treatment by a UT antagonist reduces mortality and improves cardiac function after myocardial infarction (113), decreases coronary angioplasty restenosis (114), pulmonary arterial hypertension (115) and aortic inflammation, and atherosclerosis (116).

Taken together, these data suggest that this peptide could participate rather in tissue remodeling processes during the course of the vascular disease (58) than in tonic vasculo-motor functions. This hypothesis is reinforced by the absence of modification of the vascular tone, and the appearance of a reduced metabolic syndrome and atherosclerotic lesions in UII knockout in comparison with wild-type mice (117).

Effects of UII on Cell Proliferation, Survival, and Hypertrophy

More related to tissue remodeling, the urotensinergic system exerts promitogenic effects on a number of native and recombinant cell types and hypertrophic functions only on cardiomyocytes (**Table 3**). The activation of ERK is a central element of these effects, either in cell lines transfected with cDNA encoding human UT (118) or in native cells expressing the receptor, i.e., pig renal epithelial cells (119) or rat smooth muscle cells (120). Several signaling pathways leading to the activation of ERK and cell proliferation, survival, or hypertrophy have been described in the literature. One of these pathways involves the transactivation of the epidermal growth factor receptor (EGFR) (121–123). This is often dependent on the production of reactive oxygen species (ROS) by an NADPH oxidase activated by UT (124). The ROS relieve the inhibition exerted by src homology 2-containing tyrosine phosphatase (SHP-2) on EGFR, allowing the transduction of the mitogenic signal (123, 125). This phenomenon of transactivation can also be underpinned by the activation of a disintegrin and metalloproteinase (ADAM) which cleaves the precursor of EGF, the heparin-binding EGF-like growth factor, and releases the active ligand EGFR accordingly (122, 126) (**Table 3**). The promising effects of UT are also relayed by other second messengers than previously described (PLC and PI3K), *via* receptor coupling to a pertussis toxin-sensitive $G_{i/o}$ proteins in native (45, 118, 127, 128), tumoral human rhabdomyosarcoma (129), or recombinant cell lines (130). These last observations suggest that the ability of UT to coupled $G_{i/o}$ in addition to G_q, may have provided acquisition of specific skills important for other activities than cardiovascular tone regulation.

Effects of UII on the Immune System, Relevant to Chemokine-Like Activity

There are few data concerning the link between urotensinergic and immune systems. Some studies have demonstrated the presence of UT on the surface of selected immune cells, i.e., B and NK lymphocytes, monocytes, and macrophages (145, 156), which infiltrate zones displaying high levels of immunoreactivity for UII (20). UII acts as a chemoattractant for human monocytes (145) and induces the extravasation of plasma in mice (157) and rats (158) (**Table 3**). Pro-inflammatory signals, such as tumor necrosis factor-α (TNF-α), lipopolysaccharide (LPS), or interferon-γ (IFN-γ), promote the expression of UT (145), while UII induces the secretion of cytokines, such as interleukine-6 (IL-6), in UT transfected human cardiomyocytes and lung adenocarcinoma cells (159, 160). Moreover, UII favors acetyl-coenzyme A acetyltransferase 1 activity in human monocyte (112). On coronary smooth muscle cells or endothelial cells in culture, UII increases the synthesis of inflammatory and pro-thrombotic markers like the plasminogen activator inhibitor-1, the inter-cellular adhesion molecule-1, and the tissue factor through activation of the necrosis factor NF-κB, a pro-inflammatory transcription factor (124, 161). Finally, expression of UT in human leukocytes, especially monocytes and NK cells, is strongly stimulated after exposure to LPS and requires NF-κB (145). In addition, in a mouse model of inflammatory acute liver failure, the expression of UII and

TABLE 3 | Transduction pathways associated with UT receptor activation and involved mitogenic and chemokine functions other than cardiovascular tone regulation.

Effect	Cell type	Species	Transduction pathways	Reference
Proliferation	Arterial SMC	Rabbit	PKC, src, MAPK	(110)
		Rat	RhoA, ROCK	(95)
	CHO-UT	Hamster	$G_{i/o}$, PI3K, PLC, calmodulin, MEK, extracellular Ca^{2+}	(118)
	Renal epithelial cells	Pig	Ca^{2+} (voltage-dependent channels), PKC, MAPK, ERK, c-myc	(119)
	Airway SMC	Rat	PKC, MAPK, Ca^{2+}, calcineurin	(131)
	Cardiac fibroblasts		EGFR transactivation, ERK, ROS	(121)
	Renal tubular cell line		ROS, inhibition of SHP-2, EGFP transactivation *via* HB-EGF	(122)
	SMC		Ca^{2+}, CaMK, ERK, PKD	(132)
	Endothelial precursors		ERK, p38MAPK	(133)
	Airway SMC		ERK, TGFβ	(120)
	Airway SMC	Human	NOX, ROS, ERK, p38MAPK, c-Jun, Akt, expression of PAI-1	(124)
			NOX4, ROS, FoxO3, JNK, MMP-2	(134)
	Astrocytes	Rat	PLC, intra- and extracellular Ca^{2+} (T-type channel), IP_3, $G_{i/o}$	(128)
	Fibroblastes		MAPK, VEGF expression, collagen production	(135)
	Aortic SMC		ROS, SHP-2 inhibition, EGFR transactivation	(123)
	HUVEC	Human	p38MAPK, ERK	(136)
	Cardiac precursors	Mouse	JNK, LRP6	(137)
Survival	Vascular SMC	Rat	N. D.	(138)
	Cardiomyocytes		PI3K, ERK	(139)
Hypertrophy	Cardiomyocytes-UT	Rat	G_q, Ras	(59)
			EGFR transactivation *via* HB-EGF, ERK, p38MAPK	(126)
	Cardiomyocytes		ROS, SHP-2 inhibition, EGFR transactivation	(125)
			PI3K, Akt, GSK-3β	(140)
			ROS, NADPH oxydase, Akt, GSK-3β, PTEN	(141)
Angiogenesis	HUVEC	Human	PLC, Ca^{2+}, PKC, PI3K, ERK1/2, FAK	(142)
			VEGF, endothelin-1 and adrenomedullin expression	(143)
			HIF-1, ROS, NOX-2	(144)
	Neuromicrovascular endothelial cells	Rat	N.D.	(49)
	Chick embryo chorioallantoic membrane	Chicken	N.D.	(49)
Migration, motility, adhesion	HEK293	Human	N.D.	(130)
	Monocytes	Human	RhoA, ROCK	(145)
	Endothelial progenitors	Rat	RhoA/ROCK, MLC	(146)
	Prostatic adenocarcinoma (LNCaP)	Human	RhoA, FAK	(147)
	Vascular SMC		MEK	(148)
	Vascular fibroblasts	Rat	PKC, ROCK, calcineurin, MAPK	(149)
				(150)
	Endothelial progenitors		N.D.	(151)
	Colorectal carcinoma	Human	N.D.	(152)
	Bladder cancer		N.D.	(153)
	Glioblastoma cell line		G_{13}/Rho/ROCK, $G_{i/o}$/PI3K	(154)
			Inhibition of pre-autophagic endosomes	(155)

Akt, protein kinase B; CaMK, calmodulin kinase; CHO-UT, Chinese hamster ovary line transfected with the human form of the UT receptor; EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinase; FAK, focal adhesion kinase; FoxO3, forkhead box O3; $G_{i/o}$, G_q, G_{13}, G proteins type i/o, q and 13; GSK-3β, glycogen synthase kinase 3β; HB-EGF, heparin-binding EGF-like growth factor; HIF-1, hypoxia inducible factor-1; HUVEC, human umbilical vein endothelial cells; IP_3, inositol triphosphate; LRP6, low density lipoprotein receptor-related protein 6; JNK, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; MEK, extracellular signal-regulated kinase; MLC, myosin light chain; MMP-2, matrix metalloprotease type 2; NOX, NADPH oxidase; p38MAPK, p38 mitogen-activated protein kinase; PAI-1, plasminogen activator inhibitor-1; PI3K, phosphatidylinositol-3 kinase; PKC, protein kinase C; PKD, protein kinase D; PLC, phospholipase C; PTEN, phosphatase and tensin homolog; Ras, small GTPases; RhoA, Ras homolog gene family, member A; ROCK, rho-associated protein kinase; ROS, reactive oxygen species; SHP-2, src-homology 2-containing tyrosine phosphatase; SMC, smooth muscle cells; TGFβ, transforming growth factor-β; VEGF, vascular endothelial growth factor; N.D., not determined.

UT was significantly increased in liver endothelial cells, and a pretreatment by the UT biased ligand (130) urantide decreased NF-κB activation and inflammatory cytokine (TNF-α, IL-1β, IFN-γ) expression (162).

These data indicate that UII is involved in the immune response and, notably, participates in the production of cytokines and the promotion of immune cell infiltration, suggestive of a chemokine functional activity relayed by the peptide UII, raising a more conserved role in chemotactic attraction of immune cells in pathological situations.

Chemokine Activity of UII in the Context of Tissue Remodeling and Cancer

Chemotaxis is currently known as the fundamental phenomenon highly conserved from bacteria to eukaryotic cells, implying cell directed migration along an extracellular chemical gradient (163–165), a mechanism essential for a number of physiological and pathological processes including embryogenesis and wiring of the CNS (166, 167), the immune system inflammatory response (168), angiogenesis and cancer cell metastasis, and invasion

(165, 169). The "professional" players of chemotaxis, chemokines, are subdivided into C, CC, CXC, and CX3C families, based on the number and spacing of the conserved cysteine residues in their amino termini. Members of the CXC, containing CXCL12 (stromal derived factor-1 or SDF-1) and CC including CCl2 (monocyte chemoattractant protein-1, MCP-1) or CCl5 (regulated upon activation normal T cell, RANTES) chemokine families are known to chemoattract neutrophils, T/B lymphocytes, or natural killer cells and monocytes, macrophages, or T lymphocytes, respectively (170). Through activation of chemotaxis, CXCL12, CCL2, CCL5, or CXCL1 chemokines were shown to stimulate growth, migration/invasion/metastasis as well as angiogenesis and tube formation (171, 172). The CXCL12 and its CXCR4 have long been shown to constitute a promising therapeutic based-system in pre-clinical models and in early clinical trials, but other prototypic chemokines emerge as new potential players in cancer. CCl2 together with its cognate CCR2 play key roles in cancer metastasis by sustaining cancer cell proliferation and survival, stimulating cancer cell migration and invasion, and inducing deleterious inflammation and angiogenesis (173, 174). In addition, various cancer cells produced CCl5 but also expressed CCR1, CCR3, and CCR5, suggesting autocrine/paracrine mechanisms, associated with metalloproteinase activation and invasion (175, 176).

Consistent with this, a growing number of independent studies show that UII exerts a stimulatory effect on cell migration (**Table 3**). The Rho/ROCK signaling pathway appears to play a major role in the effects of UII on the migration of rat fibroblasts (149) and endothelial progenitor cells (146) as well as human monocytes (145). In the latter case, the authors consider UII to be a chemotactic factor that acts on the reorganization of the actin cytoskeleton (**Figure 3**).

The expression of UT at the endothelial level associated with the pro-migration- and mitotic effects of UII, suggested the

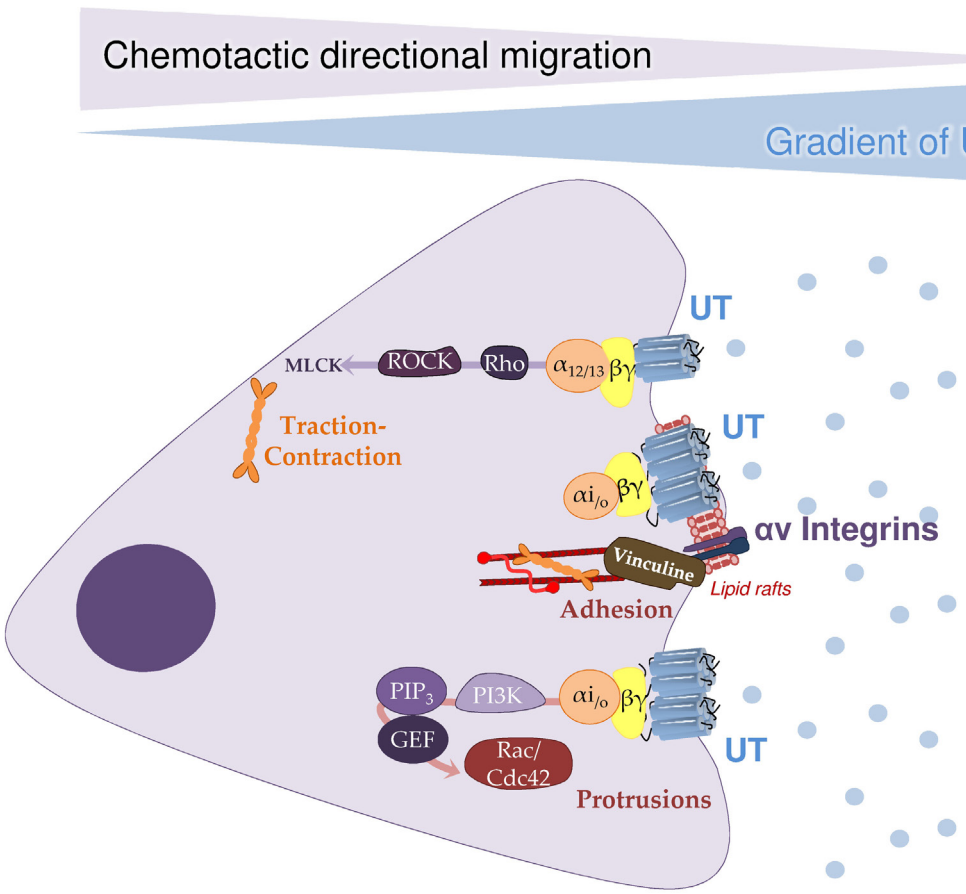

FIGURE 3 | A hypothetical outline of chemokine signaling cascade relayed by the urotensinergic system inducing cell migration. Illustration of a pathophysiological situation involving directional migration/invasion of cells expressing UT in response to a urotensin II (UII) gradient concentration. It is proposed that mobile high-affinity UT coupled to both Gαi/o and Gα13 is activated by a low concentration of UII, would promote the formation of protrusions and adhesions at the front of the cell through PI3K/PIP3/GEF/Rac/Cdc42 signaling cascade. At the back of the migrating cell, concomitant activation of G13, likely allows actomyosin contraction *via* the Rho/ROCK/MLCK pathway. To favor cell progression toward the emission source of UII, mobile or engaged UT coupled to Gi/o in lipid rafts may activate proteins responsible for the formation and maturation of focal adhesions composed of αv integrins and vinculin. Together, this pleiotropic UT associated signaling events represents a prototypic chemokine-mediated mechanism shared by P2.58 GPCRs allowing chemotactic migration. Cdc42, cell division control protein 42; GEF, guanine nucleotide exchange factor; MAP1A, microtubule-associated protein 1A; MLCK, myosin light-chain kinase; PI3K, phosphatidylinositol-3 kinase; PIP3, phosphatidylinositol 4,5-trisphosphate; ROCK, rho-associated protein kinase [from Ref. (154)].

involvement of the urotensinergic system in angiogenesis. The first evidence for a proangiogenic effect of UII was obtained by Spinazzi et al., demonstrating that UII leads to the reorganization or tubulogenesis of endothelial cells derived from rat brain microvessels, and stimulates *in vitro* angiogenesis (49). Application of UII in a gelatin implant to the chorioallantoic membrane of chick embryos evokes an increased number of blood vessels (49). Accordingly, studies on human umbilical vein endothelial cells confirmed these data (142, 144, 177) and converge toward chemoattraction of cultured endothelial cells by UII.

The major demonstration of the chemotactic role of the UII/UT system comes from studies on cancer cell lines. The expression of UII and UT is observed in numerous cell lines and tumor samples (**Table 3**), notably in extracts of adrenal gland tumors, such as adrenocortical carcinomas or pheochromocytomas (178, 179), tumors of the CNS such as glioblastomas or neuroblastomas (44, 180, 181), or tumors of muscular tissue, such as rhabdomyosarcomas (129, 182). To date, few isolated studies have investigated the role of the urotensinergic system in tumorigenesis. For example, UII has been shown to stimulate the proliferation of cells of a pulmonary adenocarcinoma cell line *in vitro* and *in vivo* in a xenograft model in immunodeficient *nude* mice (183). The same team has more recently shown that UII stimulates the release of pro-inflammatory cytokines, such as IL-6, TNF-α, or matrix metalloproteinase-9 and participates in macrophage infiltration of the tumor (160). In human cell lines derived from prostatic or colorectal tumors, application of urantide, Rho pathway inhibitor, or shRNA against UT leads to a decrease in their motility and invasiveness (147, 152). More recently, the expression of UII and UT was also observed in other solid tumors from colon, bladder, and breast (152, 153, 184). The activation of UT with the agonist UII_{4-11} in colon cancer cell lines resulted in stimulation of cell growth whereas the treatment with three biased ligand/antagonists (urantide, UPG83 and UPG85) induced growth inhibition (152). As macrophages have been associated with tumor progression, metastasis, and resistance to treatments (185), these results suggested an important role of UII in chemokine functions associated with tumor development (**Table 3**).

Definitely, the urotensinergic system appears to be involved in cancer cell motility and invasion. Indeed, our recent work demonstrated in glioma cell lines and in recombinant HEK293 cells, that activation of UT by UII involves a signaling switch through the couplings to Gα13/Rho/ROCK kinases and Gαi/o/PI3K pathways, involved in actin stress fibers, lamellipodia formation and vinculin-stained focal adhesions to initiate directional migration and cell adhesion, sequential mechanisms in tumor invasion (154). This type of mixed couplings were thus proposed for the CCl2/CCR2 system in human bone marrow stem cells in which activation of CCR2 regulates PI3K likely contributing to cell polarity and migration and Rho/ROCK leading to cell retraction (186). Moreover, we provide evidence that UT-induced inhibition of the autophagic process is also a key element in the migration of HEK293 cells expressing UT or CXCR4 as well as U87 glioblastoma cells. Autophagy inhibition after activation of UT or CXCR4 at the leading edge may also locally protect proteins involved in actin remodeling and adhesion assembly, whereas autophagy could remain active at distance from chemotactic GPCRs in order to participate in the disassembly of large focal adhesions (155). Together, the more recent pro-migratory, pro-inflammatory and invasiveness role of the urotensinergic system bring it closer to the chemokine systems, such as CXCL12/CXCR4 or the CCl2/CCR2 pair, widening the therapeutic field of pathologies characterized by cellular migratory events, such development, inflammation, invasion and metastasis.

CONCLUSION

In this review, we address the putative UT chemotactic structural and functional definition under an evolutionary angle. According to the postulated evolutionary mechanism, a deletion in TM2 of an ancestral PEP receptor with the P2.59 pattern led by divergence to receptors of the G1 groups with the P2.58 pattern, including UT and chemokine receptors, such as CXCR4. In view of the evolutionary history and chemotaxic properties of UT, we propose that UII/UT may rather be considered as a new chemokine system. Indeed, even if the last decade was mainly devoted to the elucidation of the cardiovascular control by the urotensinergic system, interesting investigations on the pro-inflammatory and pro-migratory properties of UII lead us to stipulate that urotensinergic system must be now considered in a new chemokine therapeutic target in pathological situations involving cell chemoattraction.

AUTHOR CONTRIBUTIONS

HC and LD wrote the review and prepared the figures and tables. J-EJ, M-CT, FM, and PG made the bibliography to build the review and constructed the tables and figures. LP and MC participated in the clarification of the UT classification and the establishment of the UT couplings.

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