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Targeting lipid signalling in disease

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Lipids are important mediators in cancer and inflammation, and in cardiovascular, degenerative and metabolic disease. A complex protein–lipid interaction network comprising phosphoinositides, sphingolipids, steroids and other lipid-derived mediators has been uncovered over the past few years. Many of the signalling lipids may directly interact with intracellular effector proteins to trigger multiple protein kinase cascades, nuclear receptors, stimulate guanine nucleotide exchange factors and small GTPases, while others act extracellularly on GPCRs. These signals therefore control metabolism, growth, proliferation and cell migration. Here, we provide an overview of this protein-lipid signalling network, and how it can be exploited to attenuate proliferative, inflammatory and metabolic disease.

Abbreviations

5-LO, 5-lipoxygenase; ALX, lipoxin A(4) receptor; C1/2 domain, conserved region-1/2; C1P, ceramide 1-phosphate; CCR, chemokine receptor; Cer, ceramide; CerK, ceramide kinase; COX, cyclooxygenase; cPLA2, cytosolic phospholipase A2; DAG, diacylglycerol; DD, death domain; DP, prostaglandin D; EP, prostaglandin E; ER, oestrogen receptor; ERK, extracellular signal-regulated kinase; FABP4, fatty acid-binding protein-4; FcεRI, high-affinity IgE receptor; FFA, free fatty acid; FP, prostaglandin F2α; FPRL1, formyl peptide receptor-like-1; GEF, guanine-nucleotide exchange factor; GF, growth factor; Ig, immunoglobulin; IGF, insulin growth factor; IKK, inhibitor of NF-κB; Ins, insulin; Ins(1,4,5)P_3, inositol-1,4,5-trisphosphate; IP, prostacyclin PGI2; IRS, insulin receptor substrate; JNK, c-Jun N-terminal kinase; LPA, lysophosphatidic acid; LT/A4/B4, leukotriene/A4/B4; LXR, liver X receptor; mTORC, mammalian target of rapamycin complex; NSD, neutral sphingomyelinase domain; nSMase, neutral sphingomyelinase; NucR, nuclear receptor; PDK1, phosphoinositide-dependent kinase-1; PG, prostaglandin; PGH2S, prostaglandin H2 synthase; PH, pleckstrin homology; PI3K$_x$, catalytic subunit of phosphatidylinositol 3-kinase; PKB, protein kinase B; PKC, protein kinase C; PLA2/C/D2; phospholipase A2/C/D2; PPAR, peroxisome proliferator-activated receptor; PtdIns(3,4,5)P_3, phosphatidylinositol-3,4,5-trisphosphate; PtdIns(4,5)P_2, phosphatidylinositol-4,5-bisphosphate; PTEN, phosphatase and tensin homologue; pTyr, phosphorylated Tyr; PXR, pregnane X receptor; RAR, retinoic acid receptor; Rapa, rapamycin (the FKBP12–rapa complex functions as an mTOR inhibitor); Rheb, Ras homologue enriched in brain; ROS, reactive oxygen species; RXR, retinoid X receptor; S1P, sphingosine 1-phosphate; SERM, selective oestrogen receptor modulator; SH, Src homology; SHIP1, SH2 inositol 5-phosphatase-1; SM, sphingomyelin; Sph, sphingosine; SphK, sphingosine kinase; TG, triacylglycerol; TLR, Toll-like receptor; TNFα, tumour necrosis factor-α; TP, thromboxane A2/prostanoid; TSC, tuberous sclerosis; VEGF, vascular endothelial growth factor.

For simplicity, actions of extracellular lipids, such as LTs, PGs, LPA, FFA, etc., on nuclear receptors were omitted.

Contact information and acknowledgements

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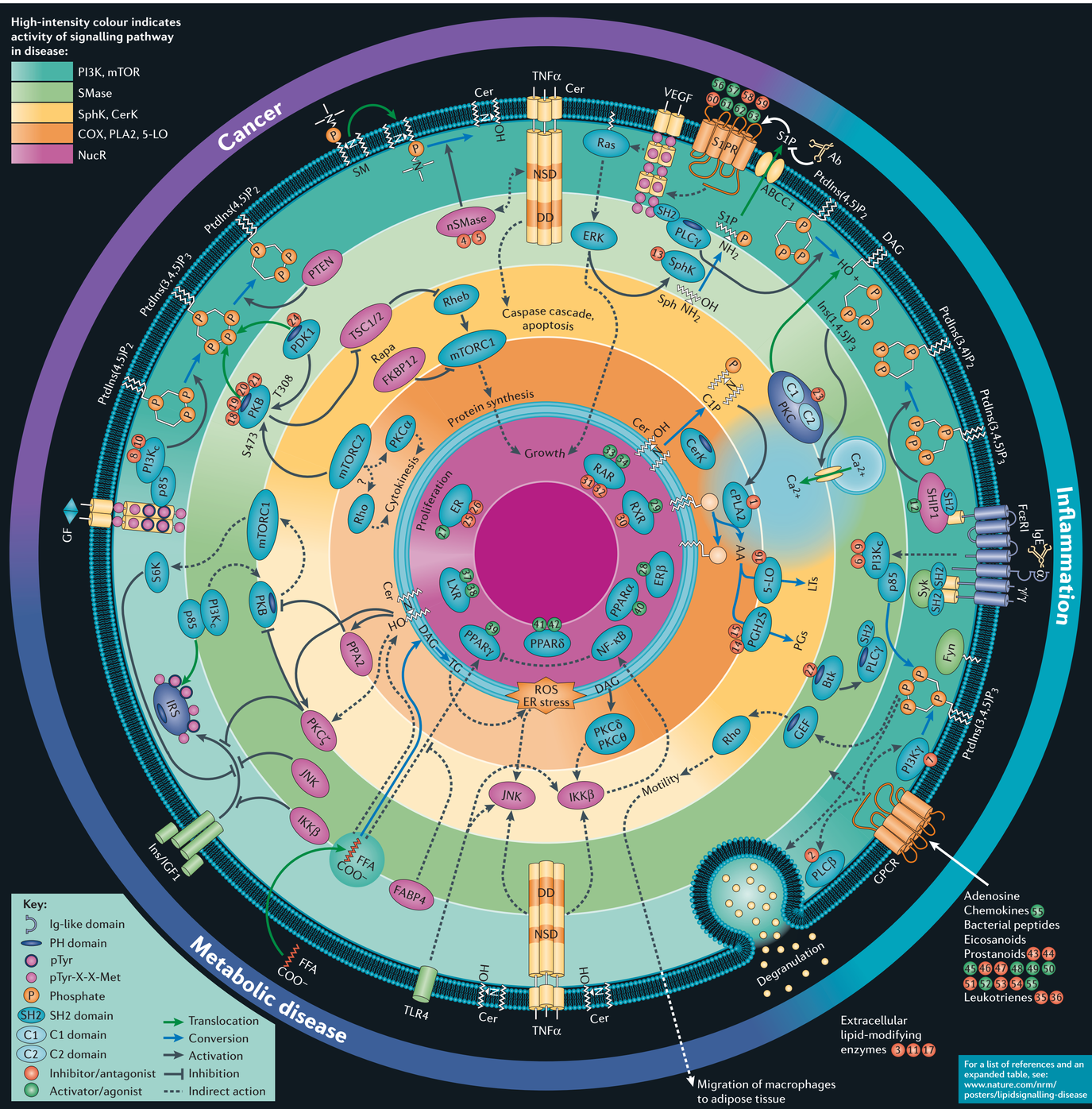

Target	Activity	Compound	Indication (status)	Refs
Lipid-modifying enzymes				
cPLA2	Inhibitor	Giripladib (PLA-695)	1 Inflammation (Phase II)	1
PLCβ1, 2, 3, 4	Inhibitor	CPR-1006	2 – (discovery)	2
Hormone-sensitive lipase	Inhibitor	Orlistat	3 Metabolic disease (launched)	–
nSMase	Selective inhibitor	Cpd 24	4 – (discovery)	3
nSMase	Inhibitor	SR33557	5 Hypertension, inflammation (Phase I)	4
PI3Kγ/δ	Dual inhibitor	TG100-115	6 Inflammation, cardiac disease (Phase I)	5
PI3Kγ	Selective inhibitor	AS-252424	7 Inflammation (preclinical)	6
PI3Kβ	Selective inhibitor	TGX-221	8 Thromboembolism (preclinical)	7
PI3Kδ	Selective inhibitor	IC87114	9 Inflammation, cancer (preclinical)	8
PI3K/mTOR	Dual inhibitor	BEZ235	10 Cancer (Phase I/II)	9
LTA4 hydrolase	Inhibitor	SC-57461A	11 Inflammation (preclinical)	10
SHIP1	Activator	AQX-MN100	12 – (discovery)	11
SphK1, 2	Inhibitor	SK-II	13 – (discovery)	12
COX1/2	Dual inhibitor	Diclofenac	14 Inflammation (launched)	–
COX2	Selective inhibitor	Celecoxib	15 Inflammation (launched)	–
5-LO	Inhibitor	Zileuton	16 Inflammation (launched)	–
Autotaxin	Inhibitor	2ccPA 16:1	17 – (discovery)	13
Lipid-signalling proteins				
PKBα	Inhibitor (ATP competitive binding)	A-443654	18 Cancer (preclinical)	14
PKBα	Inhibitor (allosteric binding)	Cpd 13b	19 Cancer (discovery)	15
PKBβ	Inhibitor (allosteric binding)	Cpd 14f	20 Cancer (discovery)	15
PKB	Inhibitor (phospholipid binding)	Perifosine	21 Cancer (Phase I/II)	16
Btk	Selective inhibitor	Cpd 1	22 Inflammation (preclinical)	17
PKCβ	Selective inhibitor	LY-333531, ruboxistaurin	23 Metabolic disease (preregistered)	18
PDK1	Inhibitor	Vernalis	24 Cancer, inflammation (preclinical)	19
Lipid receptors				
ER	SERM	Tamoxifen	25 Cancer (launched)	–
ER	SERM new generation	Lasofoxifene	26 Inflammation (preregistered)	–
ERα	Synthetic selective agonist	PPT	27 – (preclinical)	20
ERβ	Synthetic selective agonist	WAY-202041, ERB-041 (prinaberel)	28 Inflammation (Phase II)	21
RXR	Agonist	SR11237	29 – (discovery)	22
RXR	Homodimer antagonist	HX51	30 – (discovery)	23
RARα	Selective antagonist	R0-41-5253	31 Inflammation, cancer (preclinical)	24
RARβ	Selective antagonist	LE135	32 – (discovery)	25
RAR	Selective agonist	Am80 (tamibarotene)	33 Cancer, inflammation (launched)	26
RARγ	Selective agonist	R-667 (RO-3300074)	34 Inflammation (Phase II)	27, 28
LTD4 receptor	Antagonist	ICI-204219, zafirlukast	35 Inflammation (launched)	–
LTB4 receptor	Antagonist	CP-195543	36 Inflammation (Phase II)	29
LXR/PXR	Dual agonist	GW3965	37 Metabolic disease (preclinical)	30
LXRβ	Selective agonist	Cpd 3	38 – (discovery)	31
PPARγ	Agonist	Rosiglitazone	39 Metabolic disease (launched)	–
PPARα	Agonist	Cpd 36	40 – (preclinical)	32
PPARδ	Agonist	GW501516	41 Metabolic disease (Phase II)	33
PPAR	Pan agonist	Cpd 34r	42 Metabolic disease (preclinical)	34
DP2/TP receptors	Dual antagonist	Ramatroban	43 Inflammation (launched)	–
DP1 receptor	Antagonist	MK-052, laropiprant	44 Inflammation (Phase III)	35
DP2 receptor	Agonist	DK-PGD2	45 – (discovery)	36
DP2 receptor	Antagonist	TM30089	46 – (discovery)	37
EP1 receptor	Antagonist	GW-848687X	47 Inflammation (preclinical)	38
EP2 receptor	Selective agonist	CP-533,536	48 Inflammation (preclinical)	39
EP3 receptor	Selective agonist	M&B-28767	49 Inflammation (preclinical)	40
FP receptor	Agonist	Latanoprost	50 Glaucoma (launched)	–
FP receptor	Antagonist	AS-604872	51 Premature labour (preclinical)	41
IP receptor	Agonist	Cicaprost, ZK-96480	52 – (Phase II discontinued)	42
IP receptor	Antagonist	RO-1138452	53 Cardiovascular disease, inflammation (preclinical)	43
TP receptor	Antagonist	Terutroban S18886	54 Cardiovascular disease (Phase III)	44
ALX (FPRL1, CCR12)	Agonist	Cpd 43	55 – (discovery)	45
S1P1, 3, 4, 5 receptors	Agonist	FTY720	56 Inflammation, transplant rejection, cancer (Phase III)	46
S1P1 receptor	Selective agonist	AUY-954	57 – (discovery)	47
S1P1 receptor	Selective antagonist	W146	58 – (discovery)	48
S1P2 receptor	Selective antagonist	JTE-013	59 – (discovery)	49
S1P3 receptor	Selective antagonist	Example 6 in PCT	60 – (discovery)	50
S1P4 receptor	Agonist	Example 2 in PCT	61 – (discovery)	51
S1P4/5 receptor	Dual agonist	Cpd 18	62 – (discovery)	52
S1P1, 5 receptor	Dual agonist	Cpd 26	63 – (discovery)	53

The above list is a representative set of small molecules directed against lipid-modifying enzymes, lipid-signalling proteins or lipid receptors. Compounds are selected on the basis of the highest development status or greatest target selectivity.

For a list of references and an expanded table, see: www.nature.com/nrm/posters/lipidsignalling-disease