REVIEW ARTICLE

Lox Family and Their Role in Tumour Formation: An Overview

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ABSTRACT

The lysyl oxidase family has five family members which are; Lysyl Oxidase (LOX), Lysyl Oxidase Like-1 (LOXL1), Lysyl Oxidase Like-2 (LOXL2), Lysyl Oxidase Like-3 (LOXL3), and Lysyl Oxidase Like-4 (LOXL4). These are amine oxidases which are copper (Cu) dependent. The main function of these secreted enzymes is covalently crosslinking extracellular collagens and elastins, making the extracellular matrix (ECM) stable. Association with LOX family enzymes has been found in various diseases including tumours, suggesting that it may be involved in the pathogenesis of the lesions. To add to the complexity, some of the LOX family members have been linked with tumour suppression while the other members were associated with tumour promotion, progression and metastasis. Thus, this review will explore further insight into the role of LOX family in tumour formation.

Keywords: Lysyl oxidase family, LOX, lysyl oxidase-like, LOXL, tumour

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INTRODUCTION

The lysyl oxidase family consists of five family members which are; Lysyl Oxidase (LOX), Lysyl Oxidase Like 1 (LOXL1), Lysyl Oxidase Like 2 (LOXL2), Lysyl Oxidase Like 3 (LOXL3), and Lysyl Oxidase Like 4 (LOXL4). These are amine oxidases which are copper (Cu) dependent. The main function of these secreted enzymes is covalently crosslinking extracellular collagens and elastins, making the extracellular matrix (ECM) stable (1). LOX works by oxidising the peptidyl lysine to reactive semialdehyde which is peptidyl α-aminoadipic-δ-semialdehyde, that condenses and covalently crosslinking the fibrillar collagen and elastin (2). This action can be irreversibly inhibited by β-aminopropionitrile (BAPN), and also affect other LOX family activity (2–5). This is true to all LOX family members except for LOXL2 which is inhibited by the Cu chelator D-penicillamine (DPA) (6). All LOX proteins have a similar C-terminal catalytic domain which makes them the same family. The difference between them is the N-terminal signal peptide domains, which may discern their specific function. The C-terminal consists of a Cu binding site, (which comprises four histidines), a cytokine receptor-like (CRL) domain and a lysine tyrosylquinine (LTQ) cofactor (1,7,8). The N-terminal signal peptide domains can further be subdivided into two subfamilies. The first subfamily constitutes of LOX and LOXL1 as they have a similar basic peptide, which is termed propeptide (PP) (7). It is a crucial recognition site for elastin substrate (9). In both LOX and LOXL1, a proteolytic cleavage site (bone morphogenetic protein (BMP)-1) is present in between the propeptide and the LOX catalytic domain (10). However, LOX does not have proline-rich region as in LOXL1 (7).

The second subfamily constitutes of LOXL2, LOXL3 and LOXL4, in which they have similar four scavenger receptor cysteine-rich (SRCR) domains (1). SRCR domains are cell-surface proteins which have a role in the immune and host defence system. They are present on the cell surface or as secreted proteins. The proposed function of the SRCR domains is to be involved in either cell to cell binding or with other extracellular molecules (11). The protein structure of the LOX family is shown in Fig. 1.

Besides the physiological role LOX family proteins play in stabilising the ECM, which may have complex temporal and spatial expression patterns, they are also involved in pathological processes, for example by altering the tumour microenvironment (14). Having this microenvironment will then support angiogenesis, the proliferation of tumour cells, epithelial-to-mesenchymal transition (EMT), thus further invasion and metastasis (15). LOX family members modify the ECM by increasing catalytic activity, further increasing cross-linking of collagen and elastin, and consequently stiffness of the matrix, that drives malignant transformation (14). Moreover, tumour hypoxia favours the synthesis of LOX family members, thus inducing epithelial-to-mesenchymal transition (EMT) where adhesion and polarity of the cells will be disrupted, become

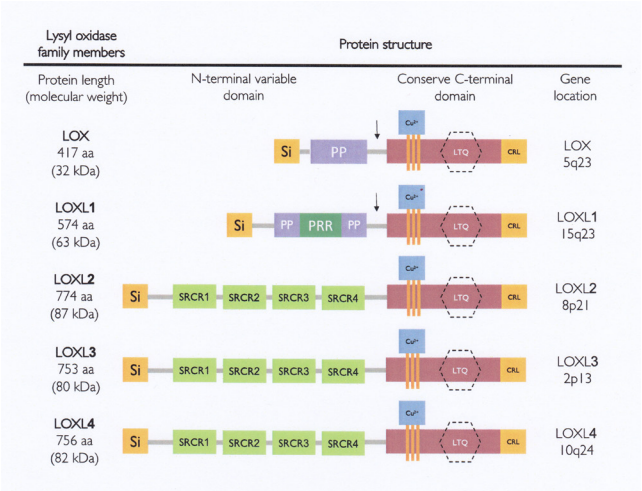

Figure 1: LOX family protein structure and gene location. LOX family shared the same C-terminal which is the catalytic domain. This conserved C-terminal has a Cu-binding domain, an LTQ cofactor and a CRL domain. There are two subfamilies according to the N-terminal characteristics; LOX and LOXL1 have propeptides (PP) but only LOXL1 has a unique proline-rich region (PRR). LOXL2, LOXL3 and LOXL4 share the same SRCR domains, which defines them as another subfamily. Arrow indicates proteolytic cleavage site. Si: Signal peptide [adapted from (8,12,13)]

mesenchymal cells with invasive properties (15). In this complex situation, a dynamic pro-tumorigenic microenvironment is created thus promoting tumour progression and metastasis to distant sites (14).

The LOX family interact with other cytokines, growth factors and cell surface receptors intracellularly and extracellularly, adding to the difficulty of understanding the function of the LOX family. Details of proposed LOX family function that is associated with cellular growth, differentiation, adhesion and apoptosis are tabulated in Table I.

Table I: Details of proposed molecular interactions of LOX family members

	Intracellular and extracellular molecular interaction	Reference
LOX	Target of transcription factor HIF1α, mediating hypoxia-induced invasion through cell to ECM adhesion and activation of integrins and FAK	(16)
	Suppress oncogenic RAS-induced cell transformation	(17,18)
	Loss of expression led to anchorage-independent growth, loss of platelet-derived growth factor (PDGF) and insulin-like growth factor 1 (IGF1)	(19)
	Regulate activity of fibroblast growth factor 2 (FGF2)	(14)
	Modulate expression and activity of oncogenes, HRAS and BCL-2	(20)
	Hydrogen peroxide, which is produced as a by-product of LOX activity, activates FAK and SRC through the activation of PI3K	(21)
	Collagen crosslinking by LOX stiffens the ECM enhancing AKT-PI3K signalling. Downstream activation of AKT stimulate NF-κB, promoting cell growth and neoplastic transformation	(14,22)
	Inhibition of LOX decrease TGFβ-stimulated p38 MAPK signalling	(23)
LOXL1	Inhibit oncogenic RAS-mediated activation of extracellular signal-regulated kinases (ERK)	(24)
LOXL2	HIF1α targets LOXL2 to mediate induction of EMT through hypoxic microenvironment	(25)
	Interact with Snail (SNAI1) to reduce E-cadherin expression	(26)
	Decrease activation of TGFβ1-mediated SMAD2 and SMAD3	(23)
	Regulate gene expression of claudin 1 (CLDN1), which encodes components of tight junctions	(27)
	Regulate gene expression of lethal giant larvae homologue 2 (LGL2), which encodes cell polarity complexes	(27)
	Negatively regulates transcription factor E2F5 which controls cell cycle	(28)
	Regulate expression of receptor activity-modifying protein 3 (RAMP3) which induces the activation of p38 MAPK and β1 integrin	(29)
	Activate SRC–FAK signalling, leading to tumour cell invasion and metastasis	(30)
LOXL3	Interact with and stabilize the transcription factor Snail (SNAI1), leading to reduced expression of E-cadherin	(26)
LOXL4	Upregulated by the transcription factors transactivator of transcription (TAT) and SP1	(31)
	Direct target of TGF- β1 and negatively regulate cell invasion by suppressing metalloproteinase 2 (MMP2) expression	(32)
	TGF-β1 mediating its function through LOXL4 *via* Smad and JunB/Fra2 proteins	(33)
	TGF-β1-dependent expression of LOXL4 might have implications in the negative feedback regulation of TGF-β- mediated cell motility	(32)

LYSYL OXIDASE (LOX)

LOX enzyme was the prototype of the LOX family to be described and is its most widely studied member. The gene is located on the chromosome 5q23 (34). The primary function of LOX is as a catalyst, where it oxidises peptidyl lysine to peptidyl α-aminoadipic-δ-semialdehyde (AAS), which is reactive semialdehyde that spontaneously condenses to covalently crosslink collagen and elastin in the ECM (7). The catalytic reaction, which requires oxygen as a cosubstrate, oxidatively removes its amino group and subsequently produces ammonia and hydrogen peroxide. Physiologically, the hydrogen peroxide produced becomes an effector of cell function contributing to cell proliferation, differentiation and migration (35). β-aminopropionitrile (BAPN) can irreversibly inhibit this reaction (2).

Intracellularly, it is present as a preproenzyme (proLOX), which contains a C-terminal catalytic domain, a PP domain and an N-terminal signal peptide. The proLOX produced in the endoplasmic reticulum and Golgi apparatus (36). ProLOX is then secreted extracellularly as a catalytically inactive enzyme. It is further cleaved to the functional LOX enzyme and LOX-PP primarily by procollagen C-proteinase (BMP-1) (36,37). Active LOX enzymes can then oxidise microfibril collagen molecules (38).

It has long been thought that the primary function of LOX was to stabilise the ECM, as evidenced by its role and cellular distribution in the cardiovascular system, gastrointestinal system, reproductive organs and various other organs such as skin, liver, lung, kidney, brain, and retina (39). The genetic absence, inhibition or down-regulation of LOX causes significant connective tissue malformation (9,40). However, in addition to these well-established functions, LOX has other biological functions which are differentiation of cells, transduction of signals and regulation of the genes (41). Even though LOX and LOX-PP have been excreted from the cell, they still can enter the cell to act on these functions (15).

LOX was described as a "ras recision gene" as it suppressed HRAS-induced transformation in a murine model, thus playing the role of a tumour suppressor gene (17,18). Later, it was found that the tumour suppressor role was undertaken by LOX-PP rather than LOX enzyme (42,43). Moreover, LOX-PP can prevent transformation and proliferation of the tumour cells, anchorage-independent growth, EMT and restoration of DNA, in addition to inducing apoptosis in various tumour cells (15). Interestingly, the mature active LOX enzyme appears to have a paradoxical relationship with LOX-PP in tumour progression. The paradoxical role of LOX as a tumour suppressor is summarised in Table II whereas tumour and metastatic promoter role are summarised in Table III.

Table II: The paradoxical role of LOX (tumour suppressor role)

		Type	Role	Reference
Tumour suppressor role	Ras-transformed NIH3T3 cells	Ras-transformed NIH3T3 cells (rat kidney fibroblast)	LOX-PP suppresses neoplastic transformation	(42)
	Breast cancer	Her-2/neu-driven breast cancer cells	LOX-PP suppresses neoplastic transformation within cell lines and inhibits tumour formation in a xenograft model	(44)
	Lung cancer	H1299 lung cancer cells	LOX-PP inactivates the signaling pathway of pro-oncogenic β-catenin	(45)
	Lung cancer	H1299 lung cancer cells PANC-1 pancreatic cancer cells	LOX-PP inhibits neoplastic transformation by suppressing the proto-oncogene Bcl-2	(20)
	Breast cancer	Breast cancer cells	Single nucleotide polymorphism (G473A) within LOX-PP impairs the tumour suppressor ability of LOX-PP in a xenograft model	(44)
	Hepatocellular carcinoma	HCC cell lines	LOX-PP inhibits cell proliferation and increases apoptosis of tumour cells	(46)
	Head and neck squamous cell carcinoma (HNSCC)	Primary tumour Primary cell lines	LOX-mRNA level was down-regulated suggesting tumour suppressor properties (not LOX-PP)	(47)

Lysyl Oxidase Like-1 (LOXL1)

LOXL1 is a part of the LOX subfamily. Of all the family members, LOXL1 is the most homologous to LOX, having a similar PP sequence. However, its proline sequence is unique to LOXL1. The human LOXL1 gene location has been identified as 15q23 (57). To date, not much is known about the function of LOXL1. It is important in the homeostasis of elastin fibres (58,59) and maturation of immature articular cartilage (60). LOXL1 single nucleotide polymorphisms have been noted to be associated with the genetic predisposition to develop ocular exfoliation syndrome and exfoliation glaucoma (61). LOXL1 was found to be epigenetically silenced in bladder cancer (24). With the reintroduction of LOXL1, there was inhibition of Ras-mediated activation of extracellular signal-regulated kinases pathway which reduced the number of bladder cancer cells indicating a tumour suppressor role (24).

Table III: The paradoxical role of LOX (tumour promoter role)

		Type	Role	Reference
Tumour promoter role	OSCC	Primary tumour tissue	Increased expression in the early stromal reaction	(48)
	Oral submucous fibrosis	Lesional tissue	Increased expression in fibrotic disease (early phase)	(48)
	OSCC	Primary cell lines	Increased expression, with induction of cell proliferation and angiogenesis	(49)
	Oral and oropharyngeal squamous cell carcinoma	High grade dysplasia, primary tumour tissue	Increased expression, with strong association with metastasis, disease progression and poor survival rate	(50)
	Breast and head and neck tumours	Primary cell lines, murine in vivo study	Expression was driven by HIF, associated with hypoxia-induced metastasis	(16)
	Breast cancer	Primary cell lines	Significant up-regulation of mRNA associated with increased invasiveness	(51)
	Breast cancer (invasive breast ductal carcinoma)	Primary tumour tissue	Overexpression in myofibroblasts, myoepithelial cells, and with reactive fibrosis within the invasive front	(52)
	Colorectal cancer	Primary tumour tissue	Significantly upregulated, increased invasiveness and metastatic potential	(53)
	Colorectal cancer	Primary and metastatic tumour tissue	Increased expression associated with tumour invasiveness	(54)
	Lung adenocarcinoma	Primary tumour tissue	Higher expression associated with invasion and poor prognosis in patients with early stage	(55)
	Hepatocellular carcinoma	Primary tumour tissue Primary cell lines	Higher expression associated with invasion and poor prognosis, regulated the expression of VEGF via p38 MAPK signalling	(56)

Lysyl Oxidase Like-2 (LOXL2)

LOXL2 is a LOX subfamily member which has four SRCR domains within their N terminal, the same as LOXL3 and LOXL4 (62). The location of the human LOXL2 gene on chromosome 8p21 (63). LOXL2 exerts similar amine oxidase activity to other LOX family but its enzyme activity is inhibited by DPA instead of BAPN (6). LOXL2 acts as a poor prognosis marker and malignant transformation through Snail-dependent and Snail-independent pathways in laryngeal squamous cell carcinoma (64). Expression of LOXL2 has increased the transformation of the breast cancer cells to the metastatic phenotype compared to the normal matched cell lines (65). Similarly, in the colon and oesophageal tumours, increased expression of LOXL2 has been seen in the less differentiated colon carcinomas (66). However, in lung adenocarcinomas reduced expression of LOXL2 is associated with the disease progression (67).

Lysyl Oxidase Like-3 (LOXL3)

LOXL3 shares the same conserved C-terminal domain with other LOX family members but has a different N-terminal domain compared to LOX and LOXL1. The N-terminal domain contains SRCR analogous to LOXL2 and LOXL4, making them another subfamily of LOX (8). The gene is situated on chromosome 2p13 (68), along with its splice variants; LOXL3-sv1 and LOXL3-sv2 (69).

They all exert amine oxidase activity but with different substrate specificity (69).

Expression of LOXL3 has been found on leucocytes, and cells of the cardiovascular system, the central nervous system, the reproductive system and the small intestine and spleen. It is also seen in the skeletal muscle, placenta and kidney, but in a lesser amount (7,9).

Loss of LOXL3 expression has been implicated in cleft palate formation, spinal deformities and it inhibits lung development in a murine model (70,71). Besides, LOXL3 (along with LOXL2) has been found to work in concert with Snail, an E-cadherin repressor, reducing cell-to-cell adhesion and promoting EMT (26). A high level of expression of LOXL3 mRNA was in relation to the poor outcome in OSCC (72).

Lysyl Oxidase Like-4 (LOXL4)

LOXL4 is the fifth member of the LOX family and a subfamily with LOXL2 and LOXL3. The LOXL4 gene is on chromosome 10q24 (8). High levels of LOXL4 mRNA has been detected in human tissues such as pancreas, testis, skeletal muscle, kidney, lung, placenta, testis and ovary. Fibroblasts demonstrate abundant expression of LOXL4, but there is a lower expression in smooth muscle cells (8).

LOXL4, like the other LOX family members, functions as an active amine oxidase and contributes to ECM stability (5). As an additional point, transforming growth factor (TGF)-β1, which is a key ECM regulator, mediates its function through LOXL4 *via* Smad and JunB/Fra2 proteins in vascular matrix remodelling (33). In head and neck squamous cell carcinoma (HNSCC), overexpression of LOXL4 mRNA is seen in the primary tumours as well as tumour cell lines, compared to the normal oropharyngeal squamous epithelium (76). Furthermore, LOXL4 gene is upregulated and amplified with significant correlation to the higher tumour stages and metastatic lymph nodes samples of HNSCC (77). Significant LOXL4 protein overexpression is also observed in the primary tumours, metastatic lymph nodes and even in the high-grade dysplastic tissues of HNSCC (78). Other than HNSCC, LOXL4 is overexpressed in gastric cancer which correlates with the tumour stages and poor survival rate (79). Upregulation of LOX, LOXL2 and LOXL4 genes are also seen in colorectal adenocarcinoma, which is associated with the hypoxic tumour microenvironment (53), suggesting that these genes may have collective roles in promoting tumour formation. However, it is also been found that LOXL4 has tumour suppressor role as it inhibits the RAS/ERK pathway, which is involved in the signalling pathway of bladder cancer cell lines (24).

CONCLUSION

Connection of the LOX family has been found in various diseases including tumours, suggesting that it may imply its role in the pathogenesis of various lesions in addition to the well-known physiological function. To add to the complexity, some of the LOX family have been affiliated with tumour suppression while the other members have the opposite relationship which is tumour promotion, progression and metastasis. LOX, being the most researched member of the LOX family, has paradoxical roles as a tumour suppressor as well as tumour and metastatic promoter. The tumour suppressor role is mainly contributed to the propeptide domain of LOX. LOXL1, even though it is the most homologous to LOX, has tumour suppressor role, but none is known about the association of LOXL1 in tumour growth. The other subfamily, LOXL2 and LOXL3 share similar tumour promoter role but not in LOXL4. LOXL4 is the recently discovered member of the LOX family, known in promoting tumour progression than inhibiting the tumour growth. However, all the results are in the combination of cancer cell lines or primary tumour sites. Further study is recommended to characterise the exact function and LOX family molecular interactions.

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