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Review

Small Leucine Rich Proteoglycans (decorin, biglycan and lumican) in cancer

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ABSTRACT

The extracellular matrix (ECM) prevents invasion of tumour cells and possesses an intrinsic mechanism to down-regulate signalling processes that promote cancer proliferation. Small Leucine Rich Proteoglycans (SLRPs) are ubiquitous ECM components involved in matrix structural organization and as such can potentially regulate cancer cell multiplication, angiogenesis and migration. Decorin, a class I SLRP that modulates collagen fibrillogenesis, also functions as a natural pan-tyrosine kinase inhibitor to reduce tumour growth. In fact, decreased decorin expression has been associated with tumour aggressiveness and lower survival. In contrast, biglycan, another class I SLRP, was highly expressed in cancer and was associated with metastatic activity and lower survival. Tissue expression of lumican, a class II SLRP, was associated with clinical outcome and appears tumour specific. Recently, decorin, biglycan and lumican were found to be potential biomarkers in bladder cancer. This review updates our current understanding on the molecular interplay and significance of decorin, biglycan and lumican expression in cancer.

1. Introduction

Cancer is a rising non-communicable pandemic and a major public health concern. According to GLOBOCAN 2018 report, an estimated 18.1 million new cancer cases and 9.6 million cancer deaths would occur worldwide in 2018 [1]. Understanding the pathophysiology and molecular mechanisms involved in tumorigenesis is essential in developing novel therapeutic agents for controlling the disease burden. A myriad of changes occurs in the tumour microenvironment that enhance tumorigenesis. This includes increased growth promoting signalling factors, altered response to growth inhibitory cues, down-regulation of protective apoptotic mechanisms, enhanced tumour perfusion and uncontrolled ability to replicate genetic material [2]. All these changes eventually lead to unrestricted and disorganized cellular proliferation, tissue invasion and metastasis [2]. The extracellular matrix (ECM) consists of noncellular components having unique properties in regulating cell behaviour. ECM also produces dynamic changes in tumour microenvironment and plays significant role in tumour progression [3]. The ECM should thus possess strong inherent regulatory mechanisms to prevent the uncontrolled proliferation of tumour cells.

Small Leucine Rich Proteoglycans (SLRPs), a diverse sub-group of proteoglycans, are involved in matrix organization and regulation of cell growth and signalling. SLRPs are ubiquitously distributed in the ECM. It consists of 17 members (Table 1) which are further categorized into five distinct classes based on their evolutionary protein conservation, leucine rich repeats (LRR), N-terminal cysteine rich clusters and chromosomal organization [4,5]. The N-terminal Cysteine rich cluster consists of four characteristic cysteine residues with intervening short amino acid consensus sequences (Table 2). Class I-III SLRPs also carry ear repeats which are formed when cysteine residues in the penultimate LRR forms disulphide bond with cysteine in the terminal LRR [4]. SLRPs are synthesised and secreted into the pericellular spaces which then gets incorporated into the tissue extracellular matrix [6]. A characteristic feature of SLRPs is their ability to interact with extracellular receptors (like tyrosine kinase receptors and toll-like receptors) facilitated by the bare β-sheets present on the concave surface of their LRR. This interaction then initiates downstream signalling that regulates cell-matrix function especially proliferation and inflammation [4,7]. Decorin is an archetypal SLRP that naturally maintains collagen fibrillar assembly and its biological interaction with various tyrosine kinase receptors downregulates the receptor activity thereby reducing the pro-oncogenic downstream signalling [4,8]. Biglycan and lumican are two-other key SLRPs that have altered expression in various cancers with diverse clinical outcome [9–12]. The molecular characteristics and

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Table 1
Classification of SLRP with respective gene symbol. The gene symbols were obtained from HUGO gene nomenclature committee (HGNC). This classification is adapted from Schaefer et al. [4].

Small Leucine Rich Proteoglycan (SLRP)	
Class I	Decorin (DCN)
	Biglycan (BGN)
	Asporin (ASPN)
	Extracellular matrix protein 2 (ECM2)
Class II	Fibromodulin (FMOD)
	Lumican (LUM)
	Proline and arginine rich end leucine rich repeat protein (PRELP)
	Keratocan (KERA)
	Osteomodulin (OMD)
Class III	Epiphycan (EPYC)
	Opticin (OPTC)
	Osteoglycin (OGTC)
Class IV	Chondroadherin (CHAD)
	Nyctalopin (NYX)
	Tsukushi (TSKU)
Class V	Podocan (PODN)
	Podocan-like protein 1 (PODNL1)

expressional significance of decorin, biglycan and lumican are mentioned in Table 2. The gene and protein expression of all three SLRPs in cancer are commonly studied using tissue samples (human and animal xenograft model), cancer cell lines, following vector mediated gene transfection into cancer cells or xenograft, gene knock out and silencing (Table 3). However, studying the circulatory (serum) expression of SLRPs can be potentially useful in determining its utility as a novel non-invasive biomarker in cancer [13]. In this review, we aim to highlight the molecular interplay and clinical expressional significance of decorin, biglycan and lumican in cancer.

2. Decorin: Tumour suppressive effect in human cancers

Decorin, a 40 kDa pan-tyrosine kinase inhibitor, is a prototype class I SLRP structurally consisting of single glycosaminoglycan (GAG) chain, either chondroitin sulfate (CS) or dermatan sulfate (DS), which is bound to the N-terminal of core protein (Fig. 1) [8]. It is secreted in the matrix by stromal cells like fibroblast, endothelial cells and myofibroblast [8]. Decorin is a natural ligand for receptor tyrosine kinases especially epidermal growth factor receptor (EGFR), insulin like growth factor-1R (IGF-1R), fibroblast growth factor receptor (FGFR) and c-met (hepatocyte growth factor receptor or HGFR); toll like receptors (TLR) on immune cells; and transforming growth factor-β (TGF-β) [4,8,14]. Decorin binds to EGFR with low affinity leading to the receptor dimerization followed by phosphorylation and activation of mitogen associated protein kinase (MAPK) resulting in downstream p21 expression that inhibits cell cycle [15]. In mammary cancer cells, by downregulating receptor tyrosine kinase HER-2 (human epidermal growth factor receptor 2) expression by nearly 40%, decorin restricted cancer proliferation and induced cellular differentiation [16]. Another mechanism to restrict tumour growth and dissemination is by impeding angiogenic growth signals. Decorin exerts an anti-angiogenic effect in tumour tissues which could have potential implications while developing future decorin based adjuvant chemotherapy [17]. Decorin inactivates receptor tyrosine kinase c-met leading to suppression of downstream β-catenin signalling which thereby reduces cancer dissemination [18]. In the tumour microenvironment, TGF-β essentially carries a complex regulatory function in modulating immunity, inflammation and cancer [19,20]. Decorin is a highly specific *in vivo* inhibitor of TGF-β. As a natural ligand, decorin sequesters and reduces the stromal bioavailability of TGF-β which is therefore incapable of initiating any downstream signalling [21,22]. Meriline et al. observed that when toll like receptors (TLR2 and TLR4) engaged with ligand decorin there is an overt production of proinflammatory protein PDCD4 (programmed cell death 4) along with suppression of miR-21 (translational inhibitor of PDCD4) [23]. It suggested that interaction of decorin with the immune cells generated a pro-inflammatory milieu that potentially restricts tumour growth. Thus, decorin interacting with various receptors in the tumour niche resulted in anti-proliferative, anti-metastatic, pro-inflammatory and angio-suppressive effects.

Decorin exhibits a guardian function in the matrix due to its onco-suppressive properties [8]. Lowest decorin immunostaining was observed in invasive breast cancer and was associated with poor clinical outcome [24]. Recently in urothelial carcinoma of bladder, we found a reduced decorin mRNA and protein expression in the tumour tissue as well as low decorin protein concentration in the serum [13]. Other human and animal model studies in colon, lung (non-small cell lung), liver, prostate and oesophageal cancers have similarly shown decreased expression suggesting that cancer proliferation necessitates the down-regulation of decorin mediated tumour suppression [25–29]. Conversely, Köninger et al. observed higher decorin mRNA and stromal immunostaining in pancreatic cancer, which probably could have resulted from a higher desmoplastic reaction in the pancreatic cancer stroma [30].

Decorin expression can be altered by certain endogenous and exogenous factors. Co-expression network analysis in colorectal cancer concurrently showed low decorin mRNA expression in association with high miR200c which suggests that miR200c could be a possible endogenous inhibitor of decorin [31]. Introduction of recombinant decorin protein and *in vitro* or *in vivo* adeno-viral gene transfer improved our understanding of decorin induced cytological, morphological and molecular changes in cancer cells. Adenovirus mediated decorin transduction into various cancer specific cell line induced p53 reprogramming which inhibited cell proliferation by activating intrinsic mitochondrial apoptotic pathway [32]. Sainio et al. observed reduced tumour cell multiplication in decorin non-expressing bladder cancer cell lines RT4 and T24 following vector mediated decorin gene transduction [33]. Co-expression of decorin and Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF) in murine CT26 xenograft resulted in similar under-expression of TGF-β along with positive modulation of both innate and adaptive immune cells [34]. It suggests that decorin expression can directly reverse the action of TGF-β over immune system and induce proliferation of immunocompetent cells possessing potent anti-tumour activity. Decorin induced intracellular destructive changes by activating autophagy and mitophagy [21,35,36]. Recently decorin mediated peg3 expression was discovered as a novel mechanism by which exogenously purified decorin induced autophagy in human umbilical cord endothelial cells (HUVEC) thereby restricting angiogenesis [35]. In MDA-MB-231 breast carcinoma cells decorin induced mitostatin mediated mitophagy and suppressed angiogenic signalling [36]. These studies show that decorin effectively suppresses cancer growth by various mechanism both *in vivo* and *in vitro* and carries the potential as a therapeutic molecule against human cancers.

Clinical outcomes in cancer patients is also influenced by decorin expression in cancer tissues. Various studies have shown that proliferating tumours expressing low levels of decorin correlated with poor patient prognosis, nodal metastases and low treatment response [27,37–41]. On the contrary, higher stromal or tumour decorin levels were associated with better survival outcome and treatment responses. Meta-analysis by Li et al. in 917 breast cancer cases showed that higher stromal decorin expression predicted good prognosis [42]. Table 3 shows the clinical significance of decorin (also biglycan and lumican) expression in various cancer studies in association with patient prognosis. It can be suggested that due to the potent anti-tumour activity by downregulating receptor tyrosine kinases and low expression in tumour inversely correlating with patient prognosis, exploring decorin from translational research to a therapeutic paradigm could have promising results. Thus, therapeutic strategies with decorin either as an intratumoral depot administration or as vector mediated intracellular delivery could be a future prospect [16].

Table 2
Molecular characteristics and cancer related expressional significance of SLRP's decorin, biglycan and lumican.

	Decorin	Biglycan	Lumican
Gene symbol (HGNC)	DCN	BGN	LUM
SLRP class	I	I	II
OMIM	125255	301870	600616
Chromosomal location	12q21.33	Xq28	12q21.33
Core protein mol. Weight	40 kDa	42 kDa	40 kDa
Glycosaminoglycan	Single CS/DS	Two CS/DS	Four KS
Immunolocalization	ECM/stromal	ECM/stromal	ECM/stromal/cytoplasm
Leucine rich repeats	10–12	10–12	6–10
Cysteine-rich cluster	CX_3CXCX_6C	CX_3CXCX_6C	CX_3CXCX_9C
Ear repeats	Present	Present	Present
Receptor interplay and Molecular signalling	- EGFR	- TLR2/TLR4	- Integrin β1
	- IGF-1R, c-met	- ↑NF-κB signalling	- ↑FAK signalling
	- ↑ p21	- ↑FAK signalling	- ↑MAPK
	- TLR2 and TLR4	- ↑Class I MHC	- ↓MMP-14
	- ↓TGF-β signalling	- ↓TGF-β	- ↓p38 & ERK1/2
	- ↑ Autophagy	- ↑ERK,	(PDAC cells)
	- ↑ Mitophagy	- ↑HIF-1α, ↑VEGF	
Molecular expression (serum, mRNA & protein)	Low	High	High
Clinical correlation	Low decorin expression in tumour tissue is associated with aggressive tumour and poor clinical outcome	High biglycan expression in tumour tissue results in enhanced metastasis, angiogenesis and poor clinical outcome	High lumican expression has poor prognosis in gastric and colon cancer while good clinical outcome in PDAC
Cancer biomarker	Plausible [13]	Plausible [13]	Plausible [13]
Therapeutic implications	Recombinant decorin can potentially reduce cancer proliferation	Targeting biglycan can probably reduce cancer invasion and metastasis	Lumican can be targeted in gastric and colon cancer

HGNC: HUGO gene nomenclature committee, OMIM: online mendelian inheritance in man., CS: chondroitin sulfate, DS: dermatan sulfate, KS: keratan sulfate, PDAC: pancreatic ductal adenocarcinoma (Symbols: ↑-enhance, ↓-reduce).

Table 3
Expressional significance of decorin, biglycan and lumican with clinical relevance observed in various cancer studies.

Authors	Cancer/cell line/xenograft	Expression	Outcome/significance
Decorin			
[24]Oda et al.	Invasive breast cancer and ductal carcinoma *in situ*	Low	Lowest decorin immunostaining associated with invasive cancer
[33]Sainio et al.	Bladder cancer	Low	Low decorin mRNA and immunostaining in invasive cancer
[25]Nyman et al.	Human colon cancer Colon cancer cell lines	Low	Low decorin mRNA and immunostaining in malignant cancer Vector mediated decorin transduction reduced colony formation *in vitro*
[28]Ji et al.	Esophageal squamous cell carcinoma	Low	Low decorin immunostaining High decorin expression clinically correlated with longer survival
[27]Hong et al.	Non-small cell lung cancer	Low	Low stromal immunoreactivity associated with poor clinical outcome
[13]Appunni et al.	Urothelial carcinoma	Low	Low circulatory (serum), mRNA and protein expression in bladder cancer Plausible cancer biomarker
Biglycan			
[10]Wang et al.	Gastric cancer	High	High mRNA and protein expression associated with poor patient prognosis
[9]Gu et al.	Colorectal cancer	High	High biglycan mRNA associated with aggressive tumour and metastasis
[59]Niedworok et al.	Bladder cancer J82 cell line	High	High biglycan mRNA associated with muscle invasive cancer Biglycan expression reduced tumour proliferation *in vitro*
[55]Liu et al.	Endometrial cancer	High	High serum, mRNA and protein expression associated with poor prognosis
[13]Appunni et al.	Urothelial carcinoma	High	High circulatory (serum), mRNA and protein expression in bladder cancer Plausible cancer biomarker
[54]Andrlová et al.	Melanoma $Bgn^{-/-}$ mice	High	High biglycan gene expression associated with poor clinical prognosis Reduced tissue stiffness and reduced invasion
[56]Jacobsen et al.	Prostate cancer	High	Positive biglycan immunostaining in 78.7% samples associated with poor clinical outcome
Lumican			
[76]Seya et al.	Advanced Colorectal cancer	High	High cytoplasmic immunoreactivity in 62.7% cancer tissue associated with lower survival
[75]de Wit et al.	Colorectal adenoma and carcinoma	High	High lumican immunostaining in 91.6% tumour samples Concurrent lumican and versican expression associated with longer survival
[68]Li et al.	Pancreatic ductal adenocarcinoma (PDAC)	High	High stromal lumican immunostaining associated with good clinical outcome
[63]Chen et al.	Gastric Cancer	High	66.4% cancer tissue show higher lumican immunostaining associated with lower survival
[11]Wang et al.	Gastric cancer	High	High lumican immunostaining (70.1%), mRNA and protein expression associated with lower survival
[13]Appunni et al.	Urothelial carcinoma	High	High circulatory (serum), mRNA and protein expression in bladder cancer. Better serum marker than decorin and biglycan.
[74] Yang et al.	Lung cancer cells	Low (siRNA)	Enhanced cancer cell invasion mediated through Rho/LIMK/cofilin pathway

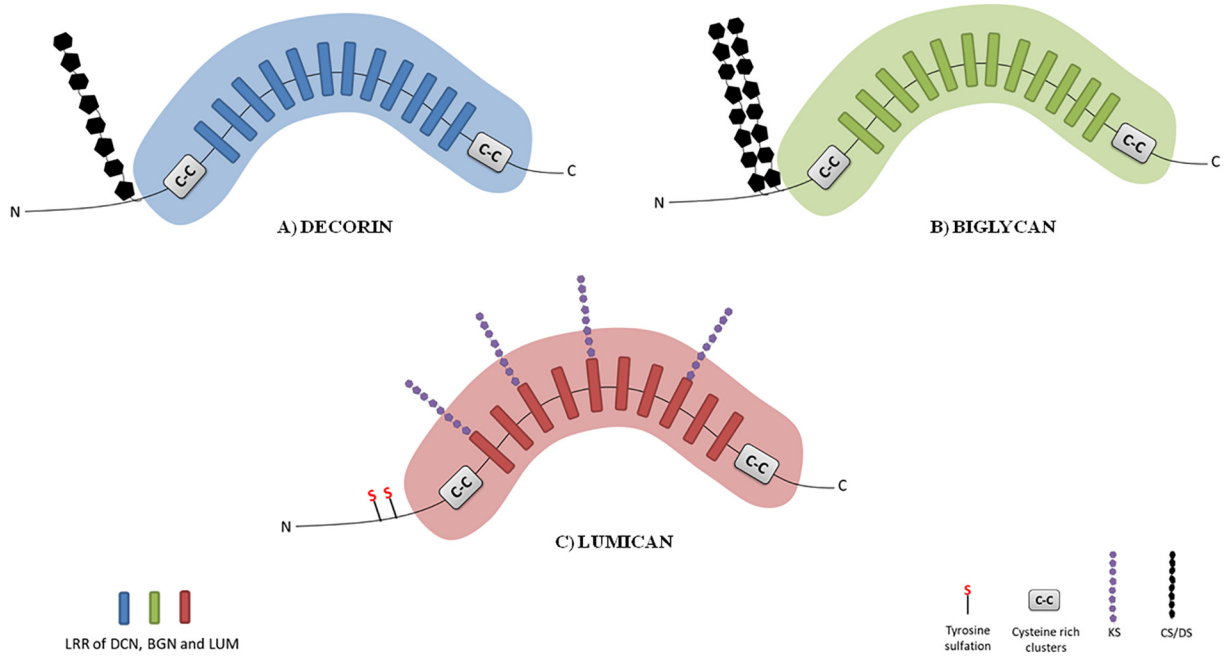

Fig. 1. Basic structure of decorin (A), biglycan (B) and lumican (C). All three SLRPs possess a curved solenoid shaped core protein comprising of 10–12 leucine rich repeat (LRR) motifs that are flanked on either side by cysteine rich clusters. Decorin consist of a single CS/DS and biglycan two CS/DS whereas lumican consist of four KS and tyrosine sulphate residues along the N-terminal domains. (CS- Chondroitin sulphate; DS- Dermatan Sulfate; KS- Keratan sulphate; GAG- Glycosaminoglycans; DCN: Decorin, BGN: Biglycan and LUM: Lumican; N: Amino terminal; C: Carboxyl terminal).

3. Biglycan: A potential marker of cancer proliferation associated with poor clinical outcome

Biglycan is a class I SLRP carrying a 42 kDa core protein that shares structural similarities with decorin (Fig. 1) [43]. It is ubiquitously expressed in ECM where it serves as a key matrix component and an essential signalling molecule [43]. Biglycan interacts with TLR2 and TLR4 on the innate immune cells to initiate inflammation *via* NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) pathway [44,45]. Biglycan mediated TLR stimulation and subsequent NF-κB expression influences cancer cell migration. Recombinant Biglycan has shown to facilitate gastric cancer cell migration through TLR (TLR2 & TLR4)/NF-κB/HIF-1α (hypoxia-inducible factor 1-α)/VEGF (vascular endothelial growth factor) mediated axis [45]. Maishi et al. has demonstrated an enhanced tumour cell migration induced by a similar biglycan-TLR (TLR2 or TLR4) interaction [46]. On the contrary, biglycan overexpression lowered tumorigenic potential by combination of Class I MHC (major histocompatibility complex) upregulation and TGF-β suppression thereby recruiting immunocompetent immune effector cells [47]. Thus, biglycan could alter tumour proliferation by modulating the receptors and cellular expression molecules within the tumour microenvironment.

Molecular mechanisms in cancer induced by biglycan are still unclear. Biglycan upregulation in cancer stroma has been associated with cell proliferation, cell migration, metastasis and angiogenesis [44,45,48]. siRNA silencing of biglycan in HTC116 colon cancer cells has shown reversal effect characterized by cell cycle arrest, lower cell migration and enhanced apoptosis [48]. Biglycan overexpression in colon cancer cells imparted chemoresistance and lower apoptotic potential through expression of NF-κB [49]. TLRs can intrinsically activate cellular pathway involved in inflammation and tumour migration which involves angiogenesis [45,50]. HUVEC treated with recombinant biglycan resulted in enhanced interaction between transcription factor HIF-1α and VEGF promoter [45]. It is a potent angiogenic stimulus effected by the biglycan/TLR/NF-κB pathway [45]. Xing et al. transfected colon cancer cell lines (HCT116 cells) with biglycan over-expressing vectors and observed significant VEGF overexpression along with enhanced activity of extracellular signal-regulated kinase (ERK) signalling pathway [51]. Other mechanisms like epigenetic modifications and reactive oxygen species (ROS) mediated dysregulation especially in the tumour endothelial cells (TEC) have effect on cancer dissemination [46,52]. Biglycan gene (Bgn) promoter demethylation in the highly metastatic tumour endothelial cells enhanced biglycan expression transcriptionally for a considerably longer time period which further promoted metastasis [46]. Also, nuclear factor erythroid 2-related factor 2 (NRF2) dysregulation induced by ROS in the tumour endothelial cells (TEC) promoted biglycan mediated pro-angiogenic signalling and TEC motility [52]. In metastatic gastric cancer cells, biglycan upregulated FAK (focal adhesion kinase) signalling facilitates cell motility and angiogenesis [53]. Correspondingly by enhancing p38 MAPK (mitogen-activated protein kinase) signalling pathway it inhibits cellular apoptosis in colon cancer cells [50]. By altering the expression of ECM cell adhesion molecules like integrin-β1, biglycan escalated the proliferation of melanoma cells [54]. These studies show that biglycan over-expression in the tumour microenvironment propagated cancer cell proliferation by modifying the intracellular signalling and ECM milieu. Thus, from a molecular perspective biglycan could be considered as a potential anti-cancer target to limit tumour angiogenesis and invasion in invasive and metastatic cancers.

From a clinical perspective, studies on human cancers showed higher biglycan expression in cancer tissue is associated with tumour invasiveness [9,10,54–56]. Recently in urothelial carcinoma of bladder, we found a significant higher serum concentration along with transcriptional and translational overexpression of biglycan in the tumour tissue [13]. Also, colorectal cancers expressing high biglycan as compared to their adjacent normal stroma positively correlated with poor differentiation and tissue metastasis [9]. Similarly, biglycan over-expressing endometrial cell lines (Ishikawa and AN3CA) displayed enhanced invasiveness and migration [57]. Unlike decorin, cancer cases showing overexpression of biglycan is also associated with poor clinical outcome. Worse clinical staging and enhanced nodal and distant metastasis with lower 5-year survival was observed in high biglycan expressing oesophageal squamous cell carcinoma [58]. Wang et al. found higher biglycan expressing gastric cancer to be associated with

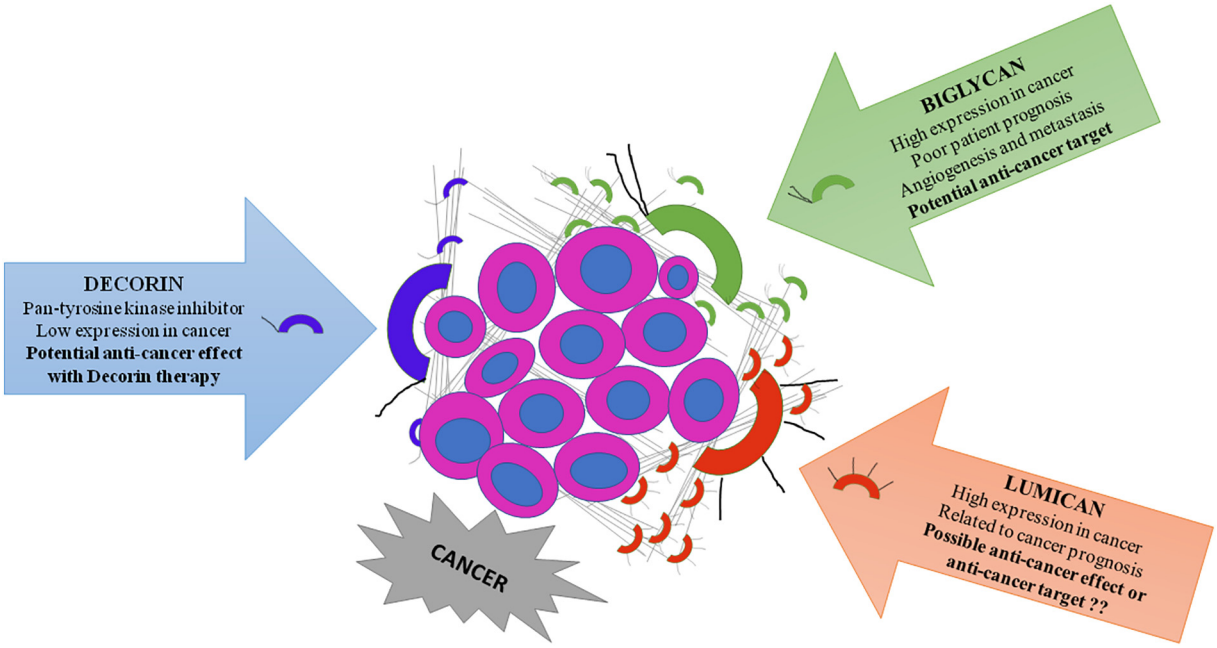

Fig. 2. Future prospects in cancer therapy with SLRPs decorin, biglycan and lumican.

metastasis, high relapse rate and low survival as compared to biglycan negative tumours [10]. Interestingly Niedworok et al. found higher biglycan expressing urothelial carcinoma (J82) cells showing reduced proliferative changes even though high mRNA expression in malignant tissue samples positively correlated with muscle invasiveness [59]. Overall higher expression in cancer correlating with pro-malignant potential and poor clinical outcome characterizes biglycan as a plausible therapeutic target in future cancer trials.

4. Lumican: Clinical outcome in high lumican expressing cancer is tumour specific

Lumican is a class II SLRP that has a 40 kDa core protein which contains 6-10 LRR flanked with cysteine rich clusters on either side, N-terminal tyrosine sulfation and carry four keratan sulphate GAG bound to its LRR by N-glycosylation (Fig. 1) [60]. As a ubiquitously expressed normal ECM component its expression is strikingly upregulated in various tumours especially lung, stomach, colon, pancreas and urinary bladder [11,24,61–63]. Functional enrichment analysis in gastric cancer genomic data showed an upregulation of lumican gene expression with relation to ECM interactions [64]. We earlier determined lumican in comparison to decorin and biglycan as a better circulatory (serum) biomarker in urothelial carcinoma of bladder [13].

Lumican is observed to modulate tumour growth and progression by different mechanisms but there is still a gap in our understanding regarding lumican expression and cancer invasion. Recently lumican signalling *via* downstream activation of FAK and MAPK have been identified [11,65]. Lumican which is highly expressed in the gastric cancer associated fibroblasts (CAF) enhanced cancer growth by activating the integrin β1 mediated FAK signalling pathway [11]. A similar FAK signalling overactivity was observed in biglycan expressing gastric cancer associated with enhanced cancer metastasis and angiogenesis [53]. This observation implies FAK signalling to be an essential common link between biglycan and lumican mediated cancer cell dissemination. Silencing of lumican reduced the invasiveness of colon cancer SW480 and HCT-8 cells and significantly deactivated MAPK signalling [65]. Nevertheless, some studies are showing a contradictory action of lumican than mentioned earlier therefore suggesting that its molecular expression and clinical outcome should be interpreted in a tumour specific manner. In prostate cancer, lumican diminished *in vitro* cyto-morphological changes required for tumour migration and invasion [12]. In breast cancer cell lines lumican strikingly decreased cancer cell proliferation, invasive characteristics and suppressed the expression of matrix metalloproteinases and EGFR [66]. Similarly, Li et al. established reduced proliferation of pancreatic ductal adenocarcinoma (PDAC) cells and suppression of p38 and ERK1/2 mediated signalling cascade following subsequent administration of extracellular recombinant lumican [67]. Lumican also downregulates EGFR mediated Akt activity leading to reduced proliferation of PDAC cells *in vitro* [68]. Lumican *in vitro*, also lowered the activity of MMP-14 (Metalloproteinase-14), a matrix degrading enzyme that augments cancer dissemination, in high Snail (transcription factor inducing MMP-14) expressing murine melanoma cells and restricted its invasiveness [69]. Lumican binds to the catalytic domain of MMP-14 and inhibits its activity thereby reducing cancer metastasis [70]. Thus, molecular signalling linked to lumican have effect on cancer proliferation and migration in a tumour specific manner.

Lumican modulates cancer growth in the matrix in response to chemotherapeutics but with a tumour specific outcome. Lumican restricted tumour growth in melanoma mice model *in vivo* targeting both the tumour cells and matrix components by sensitising the matrix microenvironment to anti-cancer TAX-2 peptide [71]. When lumican was administered in chemotherapy treated pancreatic cell lines and xenograft models, it induced genomic damage, apoptosis, low cell survivability and autophagy inhibition [72]. Also drug resistant ovarian cell lines have shown increased expression of lumican suggesting its ability to modulate drug sensitivity [73]. Lumican also has a regulatory effect over cell migration and invasion by modulating microtubular assembly. Its low expression correlated with lower p120-catenin levels in lung cancer cells that induced cytoskeletal changes and loss of cell-cell interaction subsequently leading to cell invasion [74]. Karamanou et al. demonstrated that when low [MCF-7 (ERα+)] and high [MDA-MB-231 (ERβ+)] invasive breast cancer cell lines were treated with lumican, it induced cytomorphological changes pertaining to reversal of invasion and features of mesenchymal to epithelial cell transition, overall reducing invasive properties of cancer cells [66]. These studies show that lumican is having a protective role against tumorigenesis especially reversing pro-metastatic cytoskeletal-morphological transformations. Remarkably, clinical prognosis with high lumican expressing cancer varies in a tumour specific manner especially in colon and gastric

cancers [11,62,75,76]. Advanced colon cancer patients expressing high lumican and versican concurrently have longer survivability and good clinical outcome [75]. But on the contrary, Seya et al. earlier reported high lumican expression in advanced colorectal cancer associated with lower survival and higher metastasis [76]. Li et al. observed higher survival and low recurrence rate in surgical removed pancreatic ductal adenocarcinoma (PDAC) tumour representing higher expression [68]. In gastric cancer, prognosis is strikingly affected with high lumican expression as it is associated with lower survival and poor clinical outcome [11,62]. Because of lumicans uncertain role in cancer pathogenesis and prognosis, further conclusive evidence is required to ascertain its molecular and clinical significance in various cancer and also to establish it effectiveness as either an anti-cancer target or a therapeutic molecule that suppress tumour growth.

5. Future perspective

SLRP as key matrix proteoglycan has vital role in regulating cancer progression, which is highlighted in this review. Decorin is an established pan-tyrosine kinase inhibitor which has shown onco-suppressive properties. Recombinant decorin can be considered as therapeutic molecule against cancers having overt expression of tyrosine kinase receptors like EGFR, c-MET and IGF-1α. Earlier *in vivo* transduction studies with decorin carrying vectors have shown a significant tumour suppressor function. Thus, decorin therapy in cancer could possibly reduce tumour progression (Fig. 2). Moreover, the future prospect will be to opt the most suitable delivery mode necessary to attain optimum intra-tumour concentration and significant anti-cancer effect. Biglycan overexpression on the other side is related to enhanced angiogenesis, tumour invasion and poor patient prognosis. The effect of targeting biglycan in cancer can be evaluated by the extent of metastasis and overall patient survival. Lumican though overexpressed in cancer, it is observed to have both positive and negative correlation with tumour proliferation and patient prognosis. However, the significance of lumican expression in oncogenesis needs to be further established by studying its association with specific tumour in tandem with pre-clinical analysis and clinical outcome. Thus, utilising or targeting matricellular SLRP's like decorin, biglycan and lumican in the tumour microenvironment can be adopted as a new strategy to combat cancer.

Conflict of interest

The authors declare no conflict of interest in the current review work.

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