Cellular Signalling 66 (2020) 109487

Contents lists available at ScienceDirect

Cellular Signalling

journal homepage: www.elsevier.com/locate/cellsig

Extracellular matrix-cell interactions: Focus on therapeutic applications

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ARTICLE INFO

Keywords:
Extracellular matrix
Therapy
Cell signaling
Integrin
Growth factor
Proteoglycan

ABSTRACT

Extracellular matrix (ECM) macromolecules together with a multitude of different molecules residing in the extracellular space play a vital role in the regulation of cellular phenotype and behavior. This is achieved via constant reciprocal interactions between the molecules of the ECM and the cells. The ECM-cell interactions are mediated via cell surface receptors either directly or indirectly with co-operative molecules. The ECM is also under perpetual remodeling process influencing cell-signaling pathways on its part. The fragmentation of ECM macromolecules provides even further complexity for the intricate environment of the cells. However, as long as the interactions between the ECM and the cells are in balance, the health of the body is retained. Alternatively, any dysregulation in these interactions can lead to pathological processes and finally to various diseases. Thus, therapeutic applications that are based on retaining normal ECM-cell interactions are highly rationale. Moreover, in the light of the current knowledge, also concurrent multi-targeting of the complex ECM-cell interactions is required for potent pharmacotherapies to be developed in the future.

1. Introduction

The extracellular matrix (ECM) with its multitude of different macromolecules comprises the microenvironment of cells, providing them, above all, mechanical and structural support. In the ECM there is also a variety of other molecules such as growth factors (GFs), cytokines, chemokines, matrix-degrading enzymes, and their inhibitors. All these molecules, in various combinations, are crucially involved in the regulation of cellular phenotype and functions. For instance, several ECM macromolecules are able to bind different GFs enabling the establishment of morphogen gradients around the cells, which is a vital step especially for developmental processes [1]. Cells in turn constantly reshape and remodel the structure of the ECM in order to make their movement, proliferation and differentiation possible.

The effects of the ECM macromolecules on the regulation of cell signaling takes place either directly or indirectly. In direct regulation, the ECM macromolecules interact via integrins [2] or certain other types of cell receptors such as a receptor for hyaluronan (HA), namely CD44, and syndecans [3,4]. In indirect regulation, ECM macromolecules co-operate concurrently with several receptor molecules and GFs [5]. These interactions are further complicated by constant proteolytic degradation of the ECM macromolecules that may release matrix-bound GFs that in turn activate their signaling pathways [6,7]. An introductory summary of different cell surface receptors is presented in Fig. 1A. Further, selected example of intracellular signaling pathways is presented in Fig. 1B.

Overall, the reciprocal communication between the macromolecules of the ECM and the cells forms the basis of ontogenesis, wound healing and tissue homeostasis [8]. On the other hand, virtually all diseases are related to certain alterations in ECM structure, disturbances in ECM metabolism, and/or dysregulation in ECM-cell signaling [9–11]. In this review, we will first briefly introduce the main classes of ECM

Abbreviations: ADAMTS, a disintegrin and metalloproteinase with thrombospondin motifs; AKT, protein kinase B; CD44, cluster of differentiation 44; DDR, discoidin domain receptor; ECM, extracellular matrix; EGF(R), epidermal growth factor (receptor); ErbB, receptor tyrosine-protein kinase; ERK, extracellular-signal-regulated kinase; FAK, focal adhesion kinase; FGF(R), fibroblast growth factor (receptor); FN, fibronectin; GF(s), growth factor(s); HA, hyaluronan; HAS, hyaluronan synthase; HBD, heparin-binding domain; HGF, hepatocyte growth factor; HMW, high molecular weight; HS, heparan sulfate; HSPG(s), heparan sulfate proteoglycan(s); HYAL, hyaluronidase; IGF-I(R), insulin-like growth factor I (receptor); KRAS, Kirsten rat sarcoma 2 viral oncogene homolog; LMW, low molecular weight; MAPK, mitogen-activated protein kinase; MI, myocardial infarction; MMP, matrix metalloproteinase; NF-κβ, nuclear factor-κβ; NSCLC, non-small cell lung carcinoma; PDGF(R), platelet-derived growth factor (receptor); PG, proteoglycan; PI3K, phosphoinositide 3-kinase; PTP(s), protein tyrosine phosphatase(s); RGD, arginine-glycine-aspartic acid; RHAMM, receptor for HA-mediated motility; RKT(s), receptor tyrosine kinase(s); SLRP(s), small leucine rich proteoglycan(s); TGF-β, transforming growth factor-β; TLR(s), toll like receptor(s); VEGF(R), vascular endothelial growth factor (receptor)

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https://doi.org/10.1016/j.cellsig.2019.109487
Received 6 September 2019; Received in revised form 25 November 2019; Accepted 25 November 2019
Available online 26 November 2019

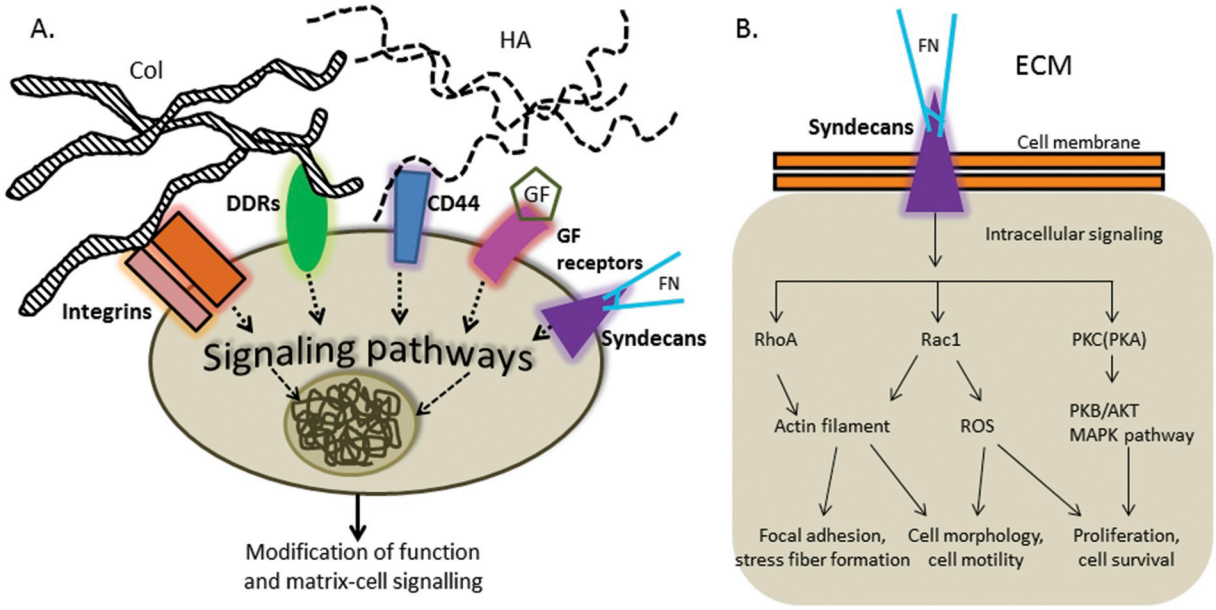

Fig. 1. Schematic overview of the cell receptor system of molecules of the ECM with special emphasis on syndecans and their signaling pathways A. Representative receptors mediating the effects of the ECM molecules inside the cells B. Intracellular signaling pathways resulting from the interaction between fibronectin and syndecans Fig. B. modified from [231]. Abbreviations: CD44, cluster of differentiation 44; Col, collagen; DDRs, discoidin domain receptor; ECM, extracellular matrix; FN, fibronectin; GF, growth factor; HA, hyaluronan; MAPK, mitogen-activated protein kinase; PKA, protein kinase A; PKC, protein kinase C; PKB/AKT, protein kinase B; Rac1, Ras-related C3 botulinum toxin substrate 1; RhoA, Ras homolog family member A; ROS, reactive oxygen species.

macromolecules and the cell receptor system of the ECM. Thereafter, we will discuss the remodeling process of the ECM. Finally, we will focus on therapeutic applications primarily targeting ECM-cell interactions that subsequently influence cell signaling.

2. Overview of ECM macromolecules

There are numerous ECM macromolecules involved in the regulation of cell signaling. The main classes are comprised of collagens, elastin, proteoglycans (PGs), hyaluronan (HA), and glycoproteins such as fibronectin (FN) and laminins. The most abundant group of ECM macromolecules is represented by the extensive family of collagens that are primarily known to provide structural support for tissues [12]. Besides collagens, elastin is a central macromolecule of the ECM where it regulates, together with fibrillin, tissue elasticity, particularly in the skin, blood vessels, lungs and ligaments [13,14]. PGs, including the small leucine rich proteoglycans (SLRPs) [15,16], and the glycosaminoglycan HA [17], are involved among their other functions in the formation of pericellular matrix and tissue homeostasis [18,19]. As mentioned above, FN [20] and laminins [21] represent non-collagenous ECM glycoproteins. Expression of FN is vital for several embryogenic processes during early development [22], and it is one of the most studied macromolecule in the ECM-cell signaling processes. Laminins are the most abundant components in basement membranes, and they are able to modulate cell adhesion, differentiation and migration [23].

One has to keep in mind that in addition to intact ECM macromolecules, their controlled proteolysis can result in enzymatic fragments, so-called matricryptins or matrikines that contain new exposed bioactive sites possessing different functional properties compared to their intact parent molecules. For instance, low molecular weight (LMW) HA fragments typically increase inflammation and are associated with e.g., tumorigenesis, while the high molecular weight (HMW) HA fragments are regarded as anti-inflammatory molecules [24].

Furthermore, ECM macromolecules can be exposed to post-translational modifications including non-enzymatic glycation, which influences ECM-cell interactions and thereby cell signaling in diseases such as diabetes and cancer [25–28]. In this sense, the glycation of FN and collagen has been shown to reduce their ability to bind to endothelial cells via their altered interaction with integrins and other cell surface receptors [26,28]. Moreover, glycated collagen has been reported to enhance tumor cell migration and invasion [25]. The glycation of the ECM macromolecules has also been demonstrated to enhance their accumulation in fibrotic processes [29].

3. Cell receptors mediating the effects of ECM macromolecules

3.1. Integrins

As mentioned above, direct regulation of cell signaling by ECM macromolecules is mediated via specific cell surface receptors. The principal ECM receptor family is represented by integrins [30]. They are transmembrane heterodimers comprised of α- (n = 18) and β-subunits (n = 8) with 24 different combinations [31–33]. The β1 subunit containing integrins comprise the largest integrin subgroup and they are overexpressed for example in various solid tumors including lung and pancreatic carcinomas [34,35]. Integrins have a tendency to cluster, which subsequently leads to multiple ligand binding [36] and the formation of molecular complexes that are composed of different scaffolding and signaling proteins [37,38]. Integrins lack enzymatic activity in their intracellular domain, so recruitment of additional signaling proteins, e.g. talin is necessary [39,40]. Integrins can also be activated from inside the cell. This is achieved via the interactions between different cytoplasmic factors and the cytoplasmic domain of integrins. The phenomenon is called inside-out signaling. The previously mentioned talin is a large cytoplasmic adaptor protein, which is of particular importance in the activation of integrins in this process [41].

Most integrins are known to bind to several different ECM macromolecules, and vice versa, many ECM macromolecules such as collagens have been shown to interact with various integrins [42,43]. Subsequently, integrins can be divided on the basis of their ligands to four groups, namely tripeptide arginine-glycine-aspartic acid (RGD), collagen, laminin, and leukocyte-specific receptors [44]. For example,

αv integrins are key receptors in the integrin-mediated regulation of tissue fibrosis, and they also prevent ECM attachment and subsequently cell motility [45,46].

Collagen integrins possess affinity for a hexapeptide, namely GFOGER-motif, in the collagen fibre [47,48]. Despite the fact that binding of specific integrins to the monomeric form of collagen type I has been studied in detail, the direct interaction between integrins and collagen fibril cores is not entirely so straightforward [49,50]. It rather seems that the interaction is regulated more by both integrin-containing suprastructures and the non-collagenous fibril periphery than the triple helical collagen molecules [51]. Nevertheless, α2β1 integrin has been designated as the major receptor for fibrillar type I collagen, and it has been reported to also bind collagen types III, IV and XI, laminins and PGs such as decorin [52,53]. All so-called collagen binding integrins are importantly involved in several physiological processes, but they are also central molecules in various pathological processes such as cancer invasion and progression [54]. For example, α2β1 integrin has been shown to play a crucial role in the maintenance of tissue homeostasis and in the promotion of cell migration [55]. Furthermore, α2β1 integrin has been shown to enhance tumor angiogenesis and the dissemination of cancer cells, particularly in hematological malignancies [56,57].

Laminin integrins have different binding specificities and affinities for various laminin isoforms [58]. In tumorigenesis, the role of laminin integrins can be either promotive or suppressive. For instance, the deficiency of α3β1 integrin in breast cancer has been shown to be tumor permissive [59], while the lack of α6β1 integrin has been demonstrated to decrease growth of hepatocellular carcinoma [60]. Leukocyte-specific integrins are primarily involved in the regulation of immune activation and inflammation [61]. From these, e.g. β2 integrins are vitally important in the regulation of monocyte, macrophage, and dendritic cell functions [62]. In addition to interacting with ECM macromolecules, integrins co-operate with different receptor tyrosine kinases (RTKs) [63–66] and protein tyrosine phosphatases (PTPs) [67–69]. They are also known to bind to CD44, which is the primary receptor for HA [70].

3.2. Other types of cell receptors for ECM macromolecules

While integrins are the most studied ECM macromolecule receptor family, other types of receptors for ECM macromolecules also exist. These include discoidin domain receptor (DDR) family for collagens [71], CD44 [72] and the receptor for HA-mediated motility (RHAMM) for HA [73], and membrane heparan sulfate (HS) PGs including syndecans for various other ECM components [74]. The DDR family contains two members, DDR1 and DDR2, which are characterized as being RTKs. They are both able to bind to various collagens, e.g. DDR1 and DDR2 use collagens I-III as their ligands, but only DDR1 is activated by collagen IV [75,76]. Abnormal DDR signaling is detected in different human diseases such as in interstitial lung diseases and cancer [77]. HA is the principal ligand for CD44, but also collagens, FN, and laminin are able to bind to it [78]. In cancer cells, the HA-CD44 complex further interacts with several RTKs such as EGFR, ErbB2, and ErbB3, subsequently activating anti-apoptotic proteins [79,80]. HA-RHAMM complex is also capable of additional interactions with RTKs like PDGFR, and it can bind to CD44-EGFR complexes as well. Both RHAMM and CD44 mediate signals that regulate cell motility, and their expression is increased in various cancer types such as in pancreatic cancer and ovarian cancer [81,82]. Regarding tissue injury and inflammation, HA interacts with toll like receptors (TLRs) 2 and 4 [83,84]. The syndecan family of cell surface HSPGs consists of four members that are able to bind numerous ECM macromolecules including collagen types I, III and V, FN, and laminin [85–87]. The interactions are formed between the syndecan HS side chain and the heparin-binding domains (HBDs) of the matrix molecules [88]. Similar to HA-receptor complexes, syndecans can act as co-receptors interacting with different RTKs such as fibroblast growth factor receptors (FGFRs), which subsequently further aid in the formation of fibroblast growth factor (FGF)-FGFR–complexes [89,90]. The functions of syndecans are markedly regulated by their ectodomain shedding, where the HS chains are cleaved by heparanases [91]. They are also able to co-operate with various integrins and other cell adhesion receptors [88]. Furthermore, syndecans exhibit fundamental roles in the regulation of cell signaling, both in normal homeostasis and in the development and progression of various human malignancies e.g., they potentiate cell invasiveness in lung adenocarcinoma and the establishment of breast cancer metastasis [92,93]. Besides syndecans, the basement membrane HSPG perlecan has been shown to act via its HS side chain as a docking receptor for GFs such as FGFs by binding them to cell membrane and further enhancing FGF-FGFR affinity during morphogenesis [94]. The interactions of ECM macromolecules, GFs, and their receptors are discussed in more detail in the next section.

3.3. Growth factors and their receptors

Besides HS containing PGs, certain other ECM macromolecules are able to directly bind soluble GFs regulating their bioavailability, signaling and distribution in tissues [95]. For example, in the liver collagen types I, III, V, and VI are able to bind hepatocyte growth factor (HGF) via their unique peptide domains [96]. PGs such as decorin can use their core protein in interacting with different GFs. Decorin was initially reported to bind transforming growth factor-β (TGF-β), thus regulating its activity [97]. Thereafter, decorin has been found to bind several other GFs including VEGF, insulin-like growth factor I (IGF−I), and PDGF [98–100]. Decorin has also been shown to bind to the receptors of the above GFs [100–102]. Its regulatory role on various processes can be context dependent, but during tumorigenesis, decorin is regarded to exhibit an oncosuppressive function, partially via its interactions with different GFs [103,104].

HA possesses versatile functions regarding different GFs. HA has been shown to constitutively regulate the activation of several RTKs including EGFR, IGF-IR, and PDGFRβ in various cancer cells such as breast, prostate and colon cancer cells [105]. In breast cancer cells, interaction of HA with CD44 has been found to activate ErbB2, subsequently resulting in the activation of phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) signaling and various anti-apoptotic events that lead to drug resistance of e.g., doxorubicin [106]. Today, the function of HA-CD44 complex mediated drug resistance has been widely studied [107]. The formation of HA-CD44 complex has also been shown to promote TGF-β-dependent cell proliferation via the interaction between CD44 and EGFR and the induction of the activation of specific mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) [108].

Fibronectin (FN), in turn, contains binding sites for GFs such as EGF, VEGF and HGF [109–111]. For example, binding of VEGF to FN activates MAPK-signaling pathway and promotes endothelial cell migration [111]. Similarly, binding of HGF to FN increases endothelial cell migration via the formation of HGF receptor-integrin interaction, and the activation of PI3 kinase pathway [110]. Recently, laminins have been found to bind various GFs including VEGF, PDFG and FGF via their HBDs [87]. Furthermore, the laminin HBD has been shown to bind to syndecans, thus emphasizing the complex network of molecular and mechanical synergy between various types of receptors and GFs even further [87,112].

4. ECM remodeling and fragmentation

The constant remodeling processes of the ECM are vital in the homeostasis of the body enabling normal cellular functions. If this process becomes dysregulated, it leads to pathological processes and finally to various diseases [9]. Hence, the expression of ECM degradative enzymes has to be very strictly controlled and regulated even

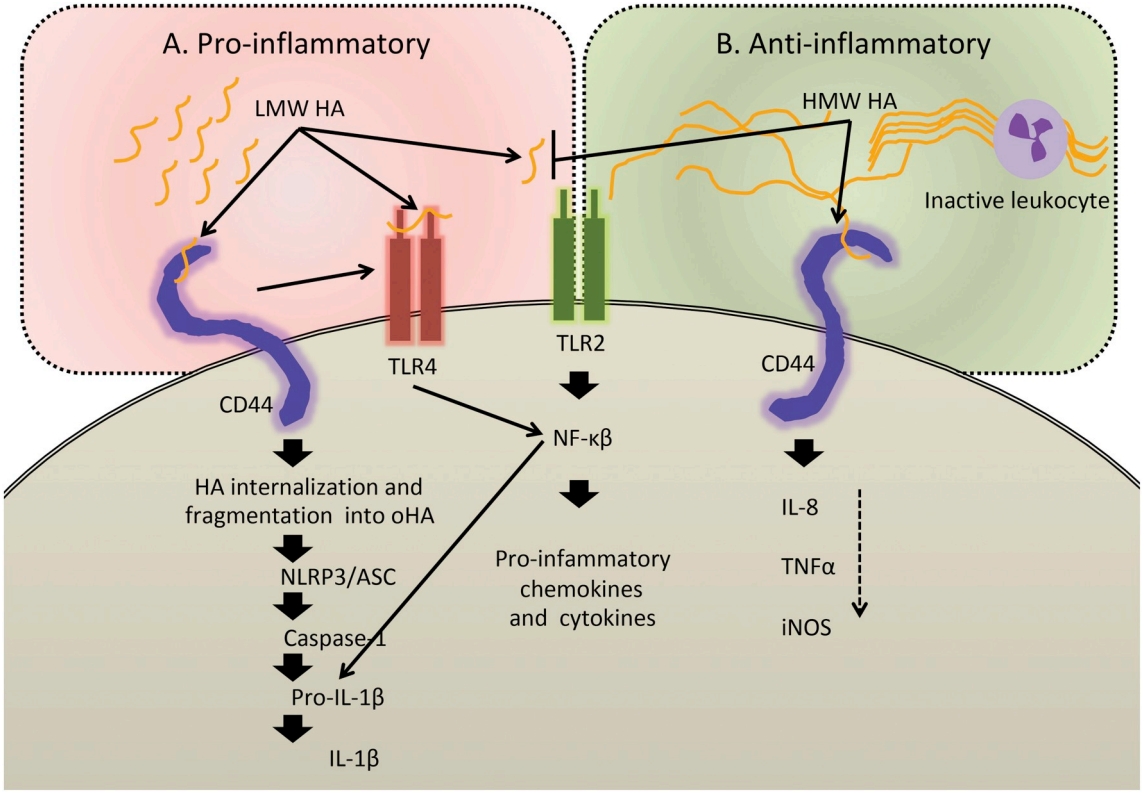

Fig. 2. Schematic overview of the role of HA fragments in inflammation A. Low-molecular weight HA is primarily a pro-inflammatory molecule. It is able to induce inflammation via binding to CD44 and TLRs, thereby augmenting inflammatory response via the activation of NLRP3/ASC inflammasome and the production of IL-1β. B. High molecular weight HA exhibits mainly anti-inflammatory properties. Its binding to CD44 reduces the production of IL-8, TNFα, and iNOS. HMW HA is also able to block the binding of LMW HA to TLR2, thereby decreasing the expression of pro-inflammatory chemokines and cytokines. The image is modified from [232]. Abbreviations: ASC, apoptosis-associated speck-like protein containing a caspase-recruitment domain; CD44, cluster of differentiation 44; HA, hyaluronan; HMW, high molecular weight; iNOS, inducible nitric oxide synthase; IL, interleukin; LMW, low molecular weight; NF-κβ, nuclear factor κβ; NLRP3, nucleotide-binding domain leucine-rich repeat-containing receptor, pyrin domain-containing-3; oHA, hyaluronan oligosaccharide; TLR, toll like receptor; TNFα, tumor necrosis factor α.

at the post-transcriptional level [113].

The enzymatic activities of different proteolytic molecules including matrix metalloproteinases (MMPs), a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS), hyaluronidases (HYALs), neutrophil serine proteases elastase and cathepsin G, are responsible for the degradation of the ECM [113–116]. MMPs and ADAMTS degrade multiple ECM macromolecules. For example, MMP-1 targets collagen type III and ADAMTS-1 degrades the PG aggrecan [117]. The tissue inhibitors of metalloproteinases (TIMPs) are endogenous inhibitors of MMPs and they regulate the release of bioactive fragments from ECM macromolecules [118].

HYALs degrade HA, generating HA fragments of various sizes and biological activities [119]. The functions of HA are mostly dependent on its molecular size. Low molecular weight (LMW) HA fragments typically increase inflammation and are associated with the promotion of tumorigenesis [24]. Furthermore, the role of LMW HA fragments as inducers of inflammation seems to be dependent on e.g. receptor expression, cell type and cellular context [120] (See Fig. 2). In pancreatic cancer, tumor cells secrete HYALs, which degrade HA into oligomers that subsequently bind to the cell's own CD44 receptors [121,122]. This induces the cleavage of the receptor and promotes tumor cell migration in a CD44-dependent manner [121].

Regarding neutrophil elastase and cathepsin G, they are able to cleave several ECM macromolecules such as collagen types I-III, IV, VI, and VIII-XI, elastin, FN and laminin [123–126]. Furthermore, these proteases are able to activate latent MMPs and to upregulate their expression [123,127]. In lung cancer, the expression of neutrophil elastase increases markedly leading to the degradation of elastin in lung parenchyma, and subsequently to the destruction of lung tissue [116]. Contradictory to the most ECM macromolecules, the turnover of elastin is almost absent in normal physiological conditions. Nevertheless, vascular aging and several pathological processes including cardiovascular and pulmonary diseases are associated with the production of large amounts of elastin peptides called elastokines [128–130]. In addition to the fragmentation of intact ECM macromolecules, the activity of different ECM degrading enzymes can lead to the release of ECM-bound GFs or to exposure of cryptic regulatory elements within the molecules [131,132]. This occurs among other things in rheumatoid arthritis, where cartilage degradation releases ECM bound GFs that increase the aggressive potential of synovial fibroblasts [131]. The release and exposure of ECM macromolecule cryptic sites can also be the result of altered mechanotransduction. This means that the cells sense the mechanical stimuli such as substrate rigidity in their microenvironment and convert them into biochemical signals [133]. Similarly to ECM remodeling, this can lead to the release of ECM-bound GFs [8].

5. Therapeutic view on ECM-cell interactions

5.1. Targeting integrins

To this day, therapeutic targeting integrins provides promising possibilities. Various therapeutic approaches have been utilized in the development of integrin-based therapeutics in cancer. These include strategies like inhibiting integrin function and inhibition of the integrin downstream signaling. These are presented in more detail with selected examples in the next paragraphs.

First of all, the integrin receptor complex can be targeted using

various agents such as antibodies, peptidic antagonists, endogenous proteins, and sulfonamide derivatives [35]. For example, the above mentioned abituzumab is a humanized monoclonal antibody targeting αv integrins [134]. It has been shown to inhibit the migration and invasion of prostate cancer cells [135]. In turn, cilengitide, which is an antagonist targeting αVβ3/αVβ5, represents the most studied integrin inhibitor [136]. Recently, its effects have been studied for example on head and neck squamous cell carcinoma [137]. Also endogenous antagonists have been tested such as the 20-kDa C-terminal fragment derived from type XVIII collagen, called endostatin, which is a supposed inhibitor of α5β1 integrin [138]. It has been shown to e.g., inhibit the tumorigenesis of hemangioendothelioma via chemokine ligand 1 downregulation and subsequent inactivation of nuclear factor-κβ (NF-κβ) [139]. Moreover, sulfonamide derivatives such as BTT-3016 can be used in blocking of α2β1 integrin activity [140]. Because the binding of vascular collagen to α2β1 integrin is an initiating event in thrombus formation, blocking of this interaction provides a possibility for novel antithrombotic therapies [141]. Another mode of α2β1 integrin signaling inhibition has been demonstrated with another sulfonamide derivative called E7820 in colon cancer, where it prevented the formation of distant metastasis [142]. More specifically, by inhibiting the binding of collagen to α2β1 integrin, E7820 inhibited the activation of PI3K/AKT/Snail signaling, and further potentiated the efficacy of known chemotherapeutic drugs such as oxaliplatin and 5-fluorouracil [142]. Moreover, the efficacy of E7820 has been tested in combination with erlotinib, an inhibitor of EGFR. The results showed synergetic antitumor effects including increased apoptosis of intratumoral endothelial cells [143].

Regarding integrin downstream signaling, also various approached have been tested. As mentioned in the Section 3.1, integrins lack enzymatic activity, so their intracellular signaling is based on cytoplasmic adapter proteins and protein kinases. Focal adhesion kinase (FAK) is a major integrin-dependent tyrosine phosphorylated protein, and thus provides a promising therapeutic target particularly in cancers e.g., colorectal cancer [144]. Hence, different FAK inhibitors have been developed including mitoxantrone, TAE-226 (Novartis), and PF-573,228 (Pfizer), which all specifically block auto-phosphorylation of FAK, and subsequently decrease viability of cancer cells [145,146]. In triple-negative breast cancer, the use of a secreted extracellular protein named tubulointerstitial nephritis antigen-like 1 has shown to be able bind integrins α5β1 and αvβ1, and EGFR, and subsequently to inhibit FAK and EGFR mediated signaling pathways leading to suppression of cancer growth and metastasis [147]. Regarding fibrosis, a known antidiabetic drug, metformin, has shown efficacy in the inhibition of integrin/ERK signaling pathway along with the reduction of ECM components like collagen type VI, MMP2 and MMP9 [148].

Moreover, in cancer cells the co-operation of integrins with different RTKs has been shown to contribute to the resistance of RTK-targeted therapies, including chemotherapy and radiotherapy [149]. Regarding EGFR, β1 integrins have been reported to regulate its cell surface expression, potentiate its EGF-mediated auto-phosphorylation, and modulate its overall oncogenic signaling activity in cancer cells [150]. For example, in non-small cell lung carcinoma (NSCLC) overexpression of β1 integrins has been shown to correlate with acquired resistance to gefitinib, which is an oral tyrosine kinase inhibitor targeting EGFR [151]. More precisely, it has been shown that the acquired gefitinib resistance is integrin β1-mediated and occurs via PI3/Akt pathway [152]. Overexpression of integrin β1 has also been shown to activate the FAK/tyrosine kinase/Akt pathway in pancreatic cancer cells resulting in EGFR ligand-independent cell growth and subsequently resistance to cetuximab, an intravenously administrated antibody for EGFR [153]. Nonetheless, also inhibition of EGFR signaling has been reported due to integrin-EGFR interaction [154]. In addition to EGFR, β1 and other integrins can co-operate with other RTKs including PDGFR, IGF-IR and VEGFR [149]. Integrins are also able to activate PTPs, subsequently suppressing GF receptor mediated signaling [67]. For example regarding EGFR signaling, the density-enhanced phosphatase-1, has been demonstrated to attenuate the GF signal pathway by de-phosphorylation of both EGFR and integrin cytoplasmic tail [69]. Another example is presented by T-cell PTP, which is able to attenuate signaling of several RTKs such as EGFR, VEGF, and PDGFR-β via integrin interaction [68]. These complex interactions clearly show that focusing only on integrins is not enough. Therefore, approaches targeting e.g. the disruption of integrin-RTK–complexes have been developed [155,156].

5.2. Targeting other types of cell receptors of ECM macromolecules

5.2.1. DDR family

Regarding the DDR receptor family for collagens, in theory their function could be prevented extracellularly by blocking their binding to collagen or by preventing their tyrosine kinase activity intracellularly. In addition to the known tyrosine kinase inhibitors dasatinib, imatinib, and nilotinib that block the function of both DDRs [157,158], novel DDR1 and DDR2 inhibitors have also been developed [159–161]. Indeed, in the future the use of DDR1 kinase inhibitors has potentially some role in the treatment of renal fibrosis [162], and DDR2 in osteoarthritis [161]. Furthermore, just recently the induction of autophagy by inhibiting DDR1 function was shown to sensitize glioblastoma cells to chemo- and radiotherapy [163].

5.2.2. HA receptors CD44 and RHAMM

As mentioned in the previous section, the expression of both CD44 and RHAM is increased in various cancer cells. This provides an opportunity to exploit HA as an anti-oncogenic therapeutic molecule and HA-receptor interaction as a specific target. Subsequently, HA-based nanoparticles have been tested to deliver various anti-oncogenic molecules such as Kirsten rat sarcoma 2 viral oncogene homolog (KRAS) targeted siRNA into CD44-positive cancer cells [164]. KRAS is one of the most mutated oncogenes in humans [165]. Moreover, the possibility of cancer therapy by CD44-EGFR dual-targeting has been examined with HA coated anti-cancer siRNA nanoparticles [166]. Similar to CD44, RHAMM, the other major HA receptor, has been targeted with HA-based nanotechnology. Specifically, doxorubicin (a leading anticancer anthracycline) loaded HA nanogels have been shown to increase drug uptake in and delivery to both primary and metastatic tumors via HA-RHAMM interaction [167]. Increased drug delivery has also been achieved via combined use of HYALs and chemotherapeutics [168]. This is a promising strategy particularly in cancers associated with accumulated HA such as pancreatic, breast and lung cancers [169]. For example in glioblastoma multiforme, the combined use of HYAL and temozolomide has been shown to inhibit the genesis of drug-resistant cancer stem cell population via disruption of HA-CD44 signaling pathway [170]. As for in NSCLC, blocking of HA-CD44/RHAMM signaling has been achieved via administration of triptolide, which significantly inhibits cancer cell growth, proliferation, and reduces the levels of HA synthase 2 (HAS2) and HAS3, HA, CD44, RHAMM, EGFR, Akt, and ERK [171]. In addition to the oncosuppressive applications, soluble HA has been widely explored as a therapeutic agent in wound healing and arthritis [172]. Applications for enhanced wound healing are presented in more detail in the Section 5.3 describing the targeting of ECM-GF signaling.

5.2.3. Syndecans

Extensive studies on the function of syndecans during tumorigenesis suggest them as potential targets in novel cancer therapies [173–175]. Similar to the inhibition of ECM-integrin binding, the direct blocking of syndecans could be achieved with antibodies. For example, syndecan-1 specific antibody called OC-46F2 has been shown to inhibit tumor growth in human melanoma model by abolishing the intratumoral complex formation of syndecan-1 with VEGFR-2 [176]. Moreover, since the generation of synstatin ($SSTN_{92–119}$), the inhibition of syndecan-1

signaling pathway has also been an option for therapeutic interventions [177]. For example, Synstatin has been shown to block the formation of syndecan-1-IGF-1R-αvβ3 integrin complex in hepatocellular carcinoma resulting in inhibition of both cancer cell proliferation and tumor angiogenesis [178]. Moreover, HS mimetics including PG545 and PI-88 have been used in the development of therapeutics [179–182]. Their effect is based on the potent capability of HS to inhibit heparanase activity as well as the function of HS-dependent angiogenic GFs. Specifically, PG545 can directly interact with Wnt3a and Wnt7a, thus disrupting Wnt/β-catenin signaling pathway in pancreatic cancer [180,181]. As for PI-88, it reduces the activity of VEGF and FGF, leading to attenuated tumor angiogenesis in hepatocellular carcinoma [179,182]. Contrasting effects has been obtained with HS mimetics called RGTA-4131 in brain damage after ischemic stroke, where they seemed to protect angiogenic factors VEGF-A and angiopoietin 2 from degradation, thereby increasing their bioavailability and resulting in enhanced tissue repair [183].

5.3. Targeting ECM-growth factor signaling

Different GFs would be ideal drugs for tissue regeneration and angiogenesis. However, their therapeutic use and safety is often hindered by their uncontrolled targeting, delivery and retention. For instance, in liver fibrosis increased vascularization, promotion of hepatocyte regeneration, and attenuation of fibrosis were accomplished by combining the collagen-binding peptide (TKKTLRT) to VEGF, which markedly improved the specificity of GF's targeting [184]. Other collagen peptides have been tested in association with GFs and various therapeutic agents [185]. In hypertrophic scarring and peritoneal fibrosis, blocking of TGF-β activation has been accomplished with decorin protein delivery and virus-based decorin gene therapy, respectively [186,187]. For example in the treatment of hypertrophic scarring, decorin has been found to reduce scar formation by downregulating the expression of TGF-β, collagen type I, and the levels of phosphorylated Smad2 and 3 [187]. Furthermore, the efficacy of oncolytic adenoviral vector based on decorin together with Wnt decoy receptor has been tested in desmoplastic pancreatic cancer on the basis of decorin's ability to block the activity of TGF- β [188,189] (See Fig. 3). Moreover, lentiviral transduction of a fusion gene based on collagen-binding domain and VEGF under hypoxia-inducible promoter after myocardial infarction, significantly improved cardiac function and angiogenesis in infarcted myocardium [190]. Additionally, disorders in wound healing, particularly in health-compromised patients, have been addressed with approaches employing different GFs [191]. These include adding structurally stabilized EGF and basic FGF into HA-collagen dressing matrices, or heparin-binding EGF into HA-derived hydrogels [192,193]. FN-derived peptides have been tested in wound healing and they seem to enhance PDFG-BB-stimulated granulation tissue formation [194]. Moreover, a significantly increased retention of VEGF (VEGF-A165) and PDGF-BB has been achieved by combining the GF-binding HBDs of laminin into fibrinogen generated fibrin matrix [87].

5.4. Inhibition of excess ECM degradation and glycation

Therapeutic approaches to regulate unstrained/excess ECM degradation have been under development for different inflammatory-associated diseases such as cancer, osteoarthritis, and chronic wound healing. Unfortunately, numerous off-target effects hinder the development of specific synthetic MMP inhibitors. Even the engineered endogenous MMP inhibitors, i.e. recombinant TIMPs, have not been stable and selective enough in tested animal models [195]. Thus, so far the antibiotic doxycycline remains the only MMP inhibitor that has been approved by FDA for clinical use [196]. The effect of doxycycline has been tested in rheumatoid arthritis patients, in whom it was found to inhibit the activity of MMP-8 [197]. Nevertheless, collagen-based wound dressing loaded with doxycycline has been demonstrated to attenuate the expression of MMP-2, −8, and −9 in an infected wound model [198]. In addition, a study using the dressing composed of doxycycline-collagen nanofibers has shown promising results [199]. Furthermore, novel strategies for MMP inhibitors are emerging including prion protein-linked designer TIMP-1 construction and engineered peptide macrocycles [200,201].

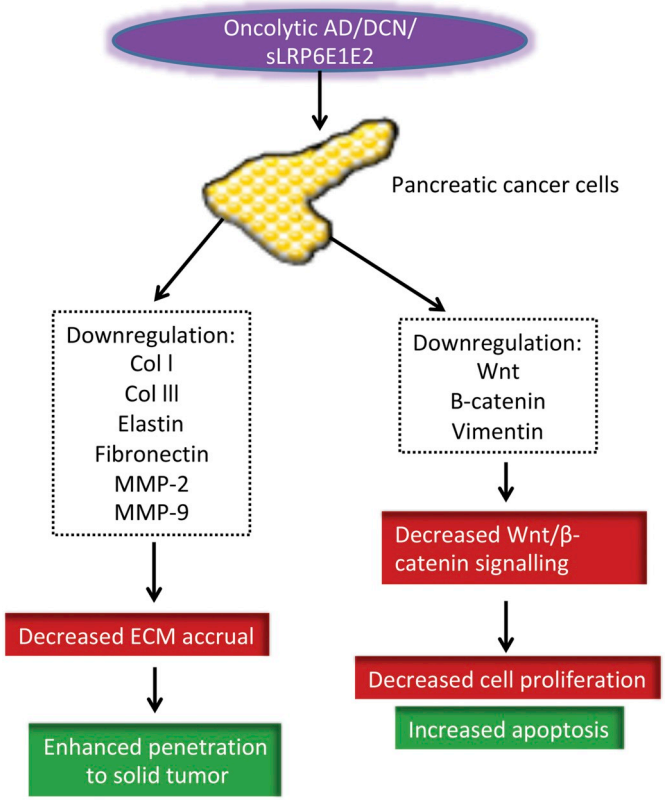

Fig. 3. Decorin-based therapy targeting pancreatic cancer cells. In the study by Li et al. [188], the oncolytic adenoviral co-transduction of decorin with Wnt decoy receptor was shown to decrease cell proliferation and increase apoptosis via downregulating Wnt/β-catenin signaling. Furthermore, the accumulation of several ECM macromolecules was concomitantly downregulated. This type of therapeutic approach would enable better delivery of cancer therapeutics to desmoplastic pancreatic tumor tissue in the future. Abbreviations: AKT, protein kinase B; Col, collagen; DCN, decorin; ECM, extracellular matrix; MMP, matrix metalloproteinase; AD, adenovirus; PI3K, phosphoinositide 3-kinase; sLRP6E1E2, soluble Wnt receptor decoy, Wnt, wingless.

Several ECM macromolecule fragments offer promising potential as therapeutics. As much array of bioactivities they exhibit, including regulation of cellular proliferation, protein expression, and angiogenesis, they provide possibilities for biomedical applications [202]. Just recently, endostatin, the fragment of collagen type XVIII, was shown to inhibit cellular proliferation, invasion and epithelial mesenchymal transition of human basal cell carcinoma [203]. More specifically, endostatin was shown to increase the expression of E-cadherin and to decrease the expression of vimentin and FN [203]. Furthermore, testing of engineered humanized recombinant endostatin has resulted in a dose-dependent inhibition of the expression and production of HMGB1, a pro-tumorigenic DNA-binding protein in NSCLC [204]. The regulatory role of endostatin in angiogenesis has been demonstrated in breast cancer, where it induces vascular normalization and subsequently improves the efficacy of chemotherapy [205]. This was shown to be mediated via inhibition of proto-oncogene tyrosine-protein kinase Src activity and its downstream signaling [205]. Furthermore, Endostar is a modified human recombinant endostatin, which has been approved in 2005 in China for treatment of NSCLC. In lung carcinoma, it was reported to downregulate HGF-induced phosphorylation of HGF receptor,

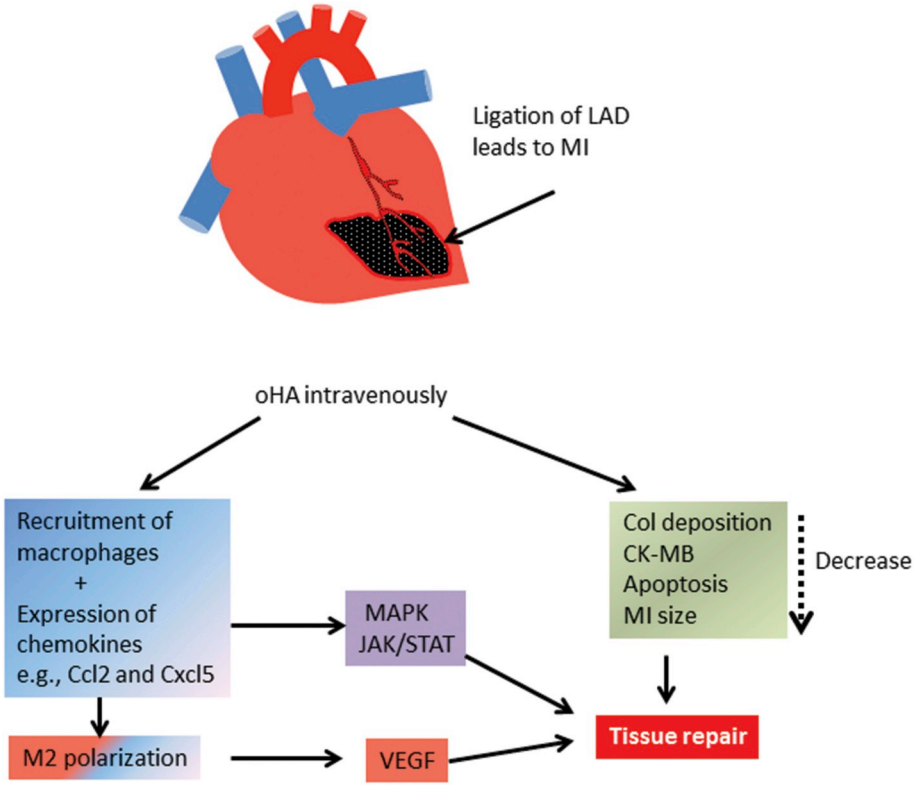

Fig. 4. Mechanisms whereby HA fragments can promote tissue reconstruction after MI, modified from [225]. Intravenous administration of oHA is able to recruit macrophages to the site of injury promoting their polarization into M2 type. It can also stimulate MAPK and JAK/STAT signaling pathway. Both mechanisms lead to the improvement of myocardial function. Intravenous administration of oHA can decrease collagen deposition, myocardial cell apoptosis and the size of infarct area. Abbreviations: Ccl2, CC-chemokine ligand 2; CK-MB, creatine kinase-muscle/brain; Col, collagen; Cxcl5, C-X-C motif chemokine 5; JAK/STAT, Janus kinase/signal transducers and activators of transcription; LAD, left anterior descending artery; M2, alternatively activated macrophage; MAPK, mitogen-activated protein kinase; MI, myocardial infarction; oHA, hyaluronan oligosaccharide; VEGF, vascular endothelial growth factor.

and to decrease cancer cell migration and invasion [206]. In addition to cancer, Endostar/endostatin has been shown to act as an anti-fibrotic molecule in different fibrosis models [207–209]. More precisely, Endostar is able to inhibit the expression of α smooth muscle actin, TGF-β, collagen type I, VEGFR1 and VEGFR1 in hepatic stellate cells and liver tissue [207,208]. Moreover, endostatin treatment has been shown to inhibit TGF-β1 and PDGF-BB-induced liver cell fibrosis by regulating the signaling of Ras homolog family member A/Rho-associated protein kinase pathways [210]. In turn, in human skin fibroblast fibrosis model, endostatin was demonstrated to inhibit hypertropic scar by modulating PDGFR-β/ERK pathway [209].

Another type of ECM macromolecule fragments is represented by elastokines, which are bioactive elastin-derived peptides with cytokine-like properties. This means that they are able to contribute to the formation of a chronic inflammatory state by stimulation of fibroblast and smooth muscle cell proliferation, by possessing powerful chemotactic activity for leukocytes, and by exhibiting as strong pro-angiogenic activities as VEGF [211,212]. Therefore, the therapeutic research regarding elastokines has been focused on the inhibition of elastase activity and on the blockage of their main receptor complex signaling pathways [212]. For example, Elafin, an endogenous inhibitor of neutrophil elastase, has been tested in inflammatory vascular injury. Besides inhibiting neutrophil elastase, it was found to inhibit protease-3 thereby exhibiting multiple anti-inflammatory properties [213,214]. Interestingly, Elafin has previously been shown to reduce inflammation by inhibiting lipopolysaccharide-induced activator protein 1 and NF-κβ activation through the ubiquitin-proteasome pathway [215]. Currently, elastase inhibitors AZD9668 and BAY 85–8501 are being tested in clinical trials of cystic fibrosis, bronchiectasis, and chronic obstructive pulmonary disease [216,217].

HA-derived oligosaccharides are known to induce the production of pro-inflammatory cytokines by binding to both CD44 and TLRs, subsequently activating NF-κβ signaling [218,219]. Consequently, the inactivation of HA fragments with a specific HA-binding peptide, Pep-1, with simultaneous use of CV-1808, a selective adenosine A2 receptor agonist, was found to decrease arthritis associated cartilage damage [220,221]. Another peptide, P15–1, which specifically mimics the HA receptor RHAMM, was demonstrated to significantly block HA oligosaccharide-mediated signaling [222]. On the other hand, the central therapeutic role of HA fragments in tissue injury/repair has long been established [84,223,224]. With respect to healing processes, HA oligosaccharides were shown to improve myocardial function after myocardial infarction (MI) by reducing apoptosis and infarct size in MI region, and by promoting myocardial angiogenesis [225] (See Fig. 4). More precisely, HA oligosaccharides can activate chemokine expression and stimulate MAPK and Janus kinase/signal transducers and activators of transcription signaling pathway leading to accelerated myocardial function reconstruction [225].

In addition to dysregulated degradation, the ECM macromolecules can face an additional challenge, namely excess post-translational glycation. This is a proteome wide problem occurring primarily in diabetic patients because of high blood glucose levels [226]. The principal therapy to prevent excess glycosylation is naturally the regulation of blood glucose levels with anti-diabetic medication. However, various other pharmaceutical agents have been tested in preclinical and clinical models for their ability to inhibit excess glycation [28,227]. Mechanistically these inhibitors target either various steps of ECM glycation process or the breakdown of already existing glucose induced collagen crosslinking [227,228]. Previously, aspirin was shown to acetylate free amino groups of proteins resulting in the prevention of glycation [229]. Thereafter, agents such as alagebrium (ALT-711) were demonstrated to break down glycosylated collagen cross-linking, thus leading to reduced aortic stiffness and improved left ventricular function [227,230].

6. Conclusion

In order to develop more potent and innovative drugs targeting the ECM-cell interactions we need better understanding of their complex signaling networks. We also must broaden our thinking to the whole microenvironment of the disease in question, and compile therapy combinations targeting simultaneously several cellular pathways. This concerns also all the different cells in the ECM. Moreover, the aspect of

translational research or the desideratum for novel preclinical models cannot be overlooked.

Author contribution section

Both authors (AS and HJ) drafted and wrote the manuscript, and also revised it.

Acknowledgements

This study was supported by the funds of Varsinais-Suomi Health District and Satakunta Central Hospital, K. Albin stiftelse, and the Finnish Cultural Foundation. Thanks to Dr. Wail Nammas for proof-reading the article.

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