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Minireview

Extracellular matrix

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A succinct overview of recent results on the biochemistry of extracellular matrix (ECM) is presented. The rapid expansion of this discipline over the best decades renders impossible to give an even approximately complete coverage of matrix biology. Some selected results concerning the four major families of macromolecules composing the ECM, that is, collagens (14 types described), elastin(s), proteoglycans and structural glycoproteins (especially fibronectin) are described. Special attention is directed to a crucial aspect of matrix biology: cell-matrix interactions. A number of cell membrane receptors were recently described mediating the two way information flow from the cells to the matrix via the 'programme' of ECM synthesis coded in the genome and unfolding during differentiation and from the ECM to the cells through the membrane receptors which contact the cytoskeleton. One of them at least, the elastin receptor was shown to be linked through a G-protein-phospholipase C-IP3 mediated relay to the regulation of intracellular calcium. Modifications of the ECM will therefore influence cell behaviour. Derangements of this informational feed back mechanisms appear to be involved in most age-related connective tissue diseases.

Connective tissue; Extracellular matrix; Collagen; Elastin; Proteoglycan; Structural glycoprotein; Fibronectin; Cell matrix interaction; Elastin receptor; Ion flux; Intracellular calcium

1. INTRODUCTION

During the last decade our knowledge about the descriptive and molecular biology of extracellular matrix (ECM) increased exponentially. An exhaustive review of only even recent work in this area would cover a whole volume. We have therefore restricted our review to selected areas and refer to recent exhaustive reviews covering the individual macromolecules of the ECM. For didactic purposes the macromolecules isolated from a variety of connective tissues (CT) of different animal species, from invertebrates to humans, can be arranged in four major categories or families: (i) collagens, (ii) elastin(s), (iii) proteoglycans (PG) and (iv) structural (or connective tissue (CT)) glycoproteins (SGP). The first two families form the fibrous scaffolding of CTs, the PGs and SGPs, the 'filling' of the interstices and the interfaces between cells and ECM. We shall mention a few aspects of recent work carried out on these substances and focus on some of those results which appear to be the most important for the relationship between the structure and function of CTs.

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Abbreviations: ECM, extracellular matrix; CT, connective tissue; PG, proteoglycans; GAG, glycosaminoglycans; SGP, structural glycoproteins; Hyp, hydroxyproline; FN, fibronectin; CS, chondroitin sulphate; DS, dermatan sulphate; KS, keratan sulphate; HS, heparan sulphate; SMC, smooth muscle cell; PAGE, polyacrylamide gel electrophoresis

2. COLLAGENS

Fourteen different collagen types are recorded today and there is no reason to believe that this is the final number [1-4]. The classical triple helix represents a quantitatively more or less important but functionally essential part of these molecules as shown schematically in Fig. 1. For the major fibrous collagens, types I, II and III (see Kühn in [2]), the relatively rigid triple helix represents the major part of the molecule. For type VI collagen more than half of its molecular weight is represented by non-triple helicoidal, glycoprotein-like structures (Timpl in [2,5]). Type IV collagen, the major constituent of basement membranes, discussed in detail by K. Kühn at the Budapest FEBS-meeting, forms a lamellar 'chicken wire'-like structure as suggested from structural and sequence studies [6-10].

The primary sequence of the α_1(IV) and α_2(IV) chains were deduced from protein chemical studies and cDNA sequencing. The α_2(IV) chain contains an excess of 43 amino acid residues, 21 of them form a disulfide-

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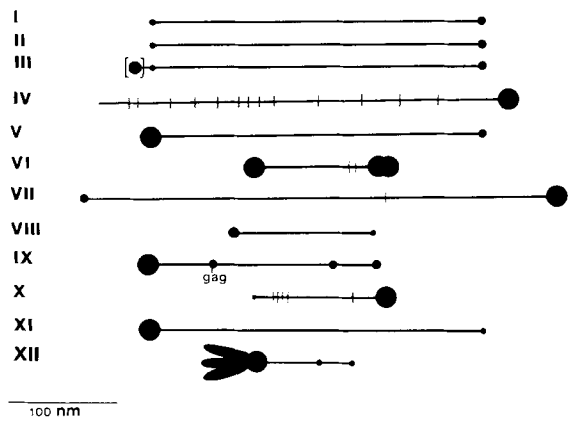

Fig. 1. Schematic representation of 12 out of the 14 known collagen molecules. The triple helical portions are represented as rods, the non-triple helical portions, mostly glycoprotein-like parts as globules or differently shaped extremities. Interruption of the triple helix is also indicated by vertical bars (i.e. for collagen type IV). (Acc. to P. Kern and [3].)

bridged loop, a unique structure in the collagen family [10]. The α_1(IV) chain contains 21 non-triplet interruptions of the collagenous domain [6]. The mode of aggregation of the non-collagenous NC1 and NC2 domains, the disulfur stabilisation of the 7 S domain enabled Kühn et al. to propose a detailed structure of the interacting ends of vicinal collagen IV molecules during polymer formation. The folding of collagen IV was studied in isolated dimers and starts from the C-terminus (NC1 domain) to proceed towards the N-terminus. The triple helix formed in a zipper-like fashion, the integrity of NC1 being essential for nucleation [9]. A special arrangement of disulfide bonds gives a peculiar clover leaf-like structure to this NC1-region [8]. The sequencing of the genes coding for the α_1(IV) and α_2(IV) chains revealed the existence of a common promoter region situated between these two genes. This is an original and efficient way to coordinate their transcription and synthesis with a promoter acting upstream and downstream [11,12]. These remarkable studies showed the great complexity of the structure of this functionally highly important collagen.

Type VII collagen, forming loosely bonded fibrous structures was identified with the anchoring fibrils of the dermo-epidermal junction [2]. Type IX collagen, occurring together with type X and XI in cartilage, was shown to bear a single glycosaminoglycan (GAG) chain, further blurring the once so clearly defined limits between the CT-macromolecules.

Relatively little is known on the function of the most recently identified collagen types. Although the use of probes enabled the identification in genomic libraries of repeating sequences of the typical Gly-x-y triplets characteristic of the collagenous triple helix, the further identification and functional study of newly identified molecules depends on phenomenological experiments using cell or tissue cultures and also on the skillful exploitation of pathological models. A good example of this is the identification of mutations or deletions in the genes of collagen type I in most cases of osteogenesis imperfecta [13].

The phylogenetic analysis of the collagen families was further advanced by Garrone's team who pioneered studies with sponge cells and showed the presence of several different genes coding for collagen α-chains at this earliest stage of phylogenetic appearance of collagens [14]. These phylogenetic studies confirmed the original proposition concerning the importance of the 54 kb elementary exon structure coding for the triple helical portions from at the beginning of the evolution of genes coding for collagen α-chains. The sponge collagen genes appear to code also for non-fibrillary collagen structures similar to type IV and earthworm cuticular collagens [14/a].

Collagens, as other matrix macromolecules, show conspicuous changes with aging. Verzar attributed the increasing thermal stability and resistance to collagenase of aging collagen fibers to increasing crosslinking [15]. The identification of lysine-derived crosslinks suggested more qualitative than quantitative modifications [16]. According to recent studies on the non-enzymatic glycation of proteins it appears probable that the Maillard reaction between reducing sugars and protein amino groups may well be responsible for this 'aging' of collagen [17]. This reaction which concerns several other proteins of the organism, is accelerated in diabetics and may well play an important role in the development of micro- and macro-angiopathies.

As far as the tissue localization of the different types of collagens is concerned, the use of monoclonal antibodies turned out to be a valuable tool. It showed, among others, the wide-spread occurrence of type VI collagen, present in many tissues [4,5,18].

The regulation of the biosynthesis of the different collagen types is still only partially understood, as is the regulation of fiber diameter and orientation [1–4]. Using explant cultures of bovine corneal stroma, it could be shown that besides collagen type I (75% of total hypro), they also contain collagens type V (8%) and VI (17%) in appreciable proportions [19,20]. Pulse-chase experiments suggested a half-life of 36 h for type I, 10 h for type V and of 6 h for type VI collagen in this tissue [20]. Ultrastructural studies indicate a close association of type I and type VI fibers, the latter probably playing an important role in the regulation of fiber diameter and orientation. The regulation of the coordinated synthesis of these collagens which results during embryonal development in the formation of the transparent stroma, cannot be repeated during wound healing in the adult animal. This results in a loss of capacity of keratocytes to reestablish the original highly organized fibrous diffraction pattern and in the loss of transparency of wounded corneas [21]. The recent original hypothesis of Fleishmajer et al. [22] tends to ex-

plain fiber width regulation by the differential and delayed loss of the C and N propeptides of types I and III pro-collagens. The presence of these propeptides during the association of the freshly extruded molecules with the growing fiber would be a guide for their lateral apposition (N-propeptides) and also a stop sign inhibiting further increase in fiber diameter (C-propeptide).

There appear to exist also long-term regulatory mechanisms as shown by the progressive increase of the type III over type I + III collagen ratio in several connective tissues with chronological aging [23]. In some aging diseases such as diabetes and also as a result of intensive UV treatment of the skin, this increase is accelerated, together with an increase of fibronectin (FN) biosynthesis [24]. Low molecular weight heparin fragments could correct this by selectively decreasing collagen III and FN biosynthesis [25,26].

Mention should also be made of the collagen triple helical sequences identified in unrelated molecules such as the acetylcholine receptor, the C_1q component of complement and the scavenger receptor of macrophages involved in the uptake of modified (oxidized, acetylated) LDL [1,27]. These examples show that genomic sequences coding for the triple helical portions of collagens were efficiently used for the anchoring of other molecules in cell membranes.

Little is known yet of the factors stabilizing the phenotype of collagen biosynthesis of differentiated cells. Chondrocytes for instance express collagens type II together with type IX, X and XI in smaller amounts. During the in vitro cultivation this phenotype is rapidly lost and collagen type I becomes predominant [4]. A similar shift in phenotype appears to occur in osteoarthritic cartilage. Cytokines such as IL-1 may play a role in this process as well as in the triggering of cartilage degradation [28].

3. ELASTIN(S)

Elastin is phylogenetically speaking the youngest matrix macromolecule, appearing in its present form only in vertebrates [29,30]. The mature elastic fibers exhibit a rubber-like (entropy-driven) elasticity. Its exceptional physical and chemical resistance (as, for instance, to boiling in 0.1 N NaOH) was attributed to the hydrophobic interactions stabilizing its tertiary (and quaternary) structure. This explains also its strong affinity for lipids and calcium. Their deposition in the mature fibers during aging and atherosclerosis leads to a progressive loss of elasticity and degradation by elastase-type proteases. The biosynthetic precursor of elastic fibers, tropoelastin, was first isolated from porcine aortas of animals raised on a copper-free diet and partially sequenced by Sandberg and associates [31]. The gene coding for tropoelastins of several species were sequenced [32–34]. The presumably single copy gene (per haploid genome) of about 40 kb situated on the long arm of chromosome 2 in humans, has one of the highest intron/exon ratios (15:1). The exons are arranged in a cassette-like fashion coding for hydrophobic or crosslinking domains [36]. Exon 36 at the 3′-end codes for a large untranslated region and 13 highly conserved C-terminal amino acids. There are several differences between the genes of human, bovine and other species investigated [36]. The 5′ flanking region contains GP1 and AP1 binding sites and a CAAT box but there is no TATA box in the promoter region. The human gene can use at least 7 different initiation sites. The resemblance of the elastin gene to other constitutively expressed genes is surprising because of its rather precise spatiotemporal expression. At least 10 bovine and 6 human exons were shown to be alternatively spliced in a non-randomly coordinated and developmentally regulated fashion [36]. Accordingly, 6 bovine and 11 human mRNAs have been characterized and at least 3 tropoelastin translation products can be seen on conventional PAGE.

The elastic fibers are associated with 'microfibrillar' structures composed of several glycoproteins [37]. The last identified high molecular weight glycoprotein apparently associated with elastic fibers is fibrillin [38]. There is no definitive agreement on the number and proportion of the different glycoproteins present in these microfibrillar structures [37].

The regulation of tropoelastin biosynthesis has been studied by several investigators. Several different splisomers can be identified in mesenchymal cell cultures (arterial smooth muscle cells, fibroblasts, chondrocytes) by immunoblots. Using fibroblast cultures from bovine ligamentum nuchae Mecham's team could show that the initiation of tropoelastin biosynthesis is developmentally regulated [39]. When elastin synthesis starts, the fibroblasts become chemotactic to elastin peptides. Fibroblasts in culture, although actively producing tropoelastin, could not incorporate it into crosslinked insoluble elastic fibers. In explant cultures, however, active incorporation of soluble precursors occurred into fibrous elastin [40]. Elastin production declined with age and with increasing population doublings. Similar results were found by Davidson's team using human skin fibroblasts [41,42]. Maximal synthesis occurs at early confluency ($32–49 \times 10^3$ molecules/cell/h), increased linearly up to 72 h (in the presence of serum) and was insensitive to inhibition of crosslinking. Biosynthesis declined after 30 population doublings and also above 70 years of age. In some cutis laxa patients a marked reduction of tropoelastin production was found in fibroblast cultures from skin biopsies, apparently because of a modification of pretranslational control [42]. Smooth muscle cells from aorta produce also large amounts of tropoelastin in cell culture and are able to crosslink it and deposit fibrous elastin resulting (in some species such as the rat) in

layered cell-matrix formation [43]. Kagan's laboratory studied peptidyl lysyloxidase catalysing the crosslinking of tropoelastin during fiber formation [44] and described many properties of this crucially important enzyme.

Recent progress in elastin biochemistry has come from the study of cell-elastin interactions. An adhesion mechanism enables mesenchymal cells (fibroblasts, smooth muscle cells) [45,46] and also highly metastatic malignant cells [47,48] to adhere strongly to the elastic fibers. The isolation of the adhesive complex from metabolically labelled fibroblasts suggested a role for a 120 kDa glycoprotein designated as elastonectin [45]. Its synthesis and cell-fiber adhesion could be 'induced' by the previous addition of soluble elastin peptides (K-elastin) suggesting a receptor mediated mechanism [45,46,48]. The existence of a receptor recognising elastin-specific sequences was also suggested by modifications of ion-fluxes in cells in presence of elastin peptides (increased calcium influx, decrease of ouabain-dependent K^+ influx) as well as the liberation of oxygen radicals and lytic enzymes (elastase) from human white blood cells [49–51]. Independently Mecham's team also arrived at the conclusion that the chemotactic effects of elastin peptides are mediated by an elastin receptor [52–54]. It could be shown that the activation of this receptor is mediated by a G-protein, IP_3 and DAG production and could be blocked by the appropriate inhibitors [55,56], abolishing Ca^{2+} influx and the induction of adhesion. Non-induced adhesion was, however, not inhibited. The ligand-specific subunit of the elastin receptor is a 65–67 kDa lectin-like protein sensitive to lactose [52–54] which was shown recently to cross-react with laminin-sequences [54]. Neither lactose nor RGD-peptides could, however, inhibit non-induced adhesion of cells to elastic fibers. The expression of the elastin receptor and of the adhesive mechanism by highly metastatic (but not by low metastatic) tumor cells [47,48] suggests a possible role for these mechanisms in the colonisation of elastin-rich tissues (lung) by such cells.

Progress has also been made in the characterisation of elastase-type proteases [57,58]. These enzymes belong to several different classes of proteases and are produced by a variety of cells. Their importance in several pathological processes (emphysema, aneurysm formation, athero-arteriosclerosis, inflammation, etc.) was demonstrated by several laboratories. Synthetic and natural elastase inhibitors are actively being investigated in the hope of their therapeutic efficiency in the above diseases [30].

4. PROTEOGLYCANS

Designated for a long time as acid mucopolysaccharides, these compounds were considered as rich in carbohydrates until molecular genetic methods together with tedious isolation procedures enabled the recognition of a variety of backbone proteins onto which the glycosaminoglycan chains were linked. The carbohydrate chains of proteoglycans (PG) were among the first well-characterized ECM components (for a review see [59,60]) which show a striking regularity of repeating sequences containing hexosamines and uronic acids (D-glucosamine, D-galactosamine, D-glucuronic acid, L-iduronic acid), *N*-acetylated sometimes *N*-sulfated and *O*-sulfated on the hexosamine sometimes on the iduronic acid moiety. The linkage to the protein portion can be (mostly) *O*- or (sometimes) *N*-glycosidic with an ordered sequence of carbohydrates at the linkage point such as Ser(Thr)-Xyl-Gal-Gal-Uron-$(disach)_n$ [59,60]. The only exception remained hyaluronate or hyaluronan as designated by Laurent and Balazs [61] with its much higher molecular weight (in the 10^6) and the absence of covalently linked protein partner. Besides the carbohydrate-rich cartilage PGs there are others with a much lower carbohydrate-to-protein ratio such as dermatan-sulfate-PG of the skin, for instance. The recognition of heparan-sulfate and chondroitin-sulfate PGs on cell membranes and basement membranes also highlighted the importance of the protein portion for membrane insertion and specific interaction purposes. Finally the recognition of specific amino acid sequences commanding the anchorage of the glycosaminoglycan chains essentially through the work of Ruoslahti's team [62] definitely focused attention on these long-neglected partners of the GAG-chains. As only the protein backbone can be directly encoded in the genome, it became logical to propose a novel nomenclature for the PGs as was done recently by Ruoslahti [62], based entirely on the specific protein partner. In his recent review he enumerates 15 different sequenced (mostly by the cDNA) core proteins containing GAG chains of the CS, DS, HS or KS type. Among the recently identified core proteins one can find representatives of the collagen family (collagen type IX), invariant chain, transferrin receptor, thrombomodulin. The recently demonstrated role of PGs in cell-cell and cell-matrix interactions focused attention on the membrane-bound HSPGs. Receptors recognising selectively some GAG-chains were postulated [63,64]. The role of tumor cell membrane PGs in metastasis formation was rendered plausible by the demonstration of a regular shift in DS/CS ratio with metastatic capacity in rhabdomyoma cell lines [25,66]. Progress was accomplished also in the understanding of the metabolic regulations of PG synthesis and degradation. The degradation by hyaluronidase-type enzymes was shown to trigger an increased hyaluronate biosynthesis in human skin fibroblasts [67]. Hyaluronane synthetase is a membrane-bound enzyme working in coordination with a receptor recognising nascent hyaluronane chains [68]. Besides their role in cell-cell and cell-matrix interactions, their function as high molecular

weight polyelectrolytes in the control of molecular traffic in the ECM and in ion equilibria is also important [59–61]. KS is the only known GAG where the uronic acid residues are substituted by galactose-residues [69]. It was suggested by Scott that the availabilitiy of O_2 may well be the limiting regulatory factor in its synthesis [70]. In tissues where the diffusion of oxygen is slow such as the corneal stroma or cartilage, the rate-limiting step in furnishing UDP-glucuronic acid could well be the oxidation of UDP-Glc, favoring the accumulation of UDP-Gal by the action of UDP-Glc-isomerase.

An important function of HSPGs is in the maintenance of selective filtration capacity of basement membranes. Their decrease with age and especially in diabetes is an important factor in the progressive loss of that capacity [71]. HSPG was also shown to act as a storage site for some growth factors (acidic and basic FGF) and to play a role in the regulation of cell proliferation. The cleavage of HS-chains from endothelial cells and their recognition by receptors on smooth muscles cells may well represent one of the regulatory mechanisms in SMC-proliferation in the arterial wall [72]. The interaction properties of PGs depend both on the protein and GAG-portions. The core protein of cartilage PGs contains lectin-like domains interacting strongly with hyaluronan sequences as well as with link proteins [59]. Sulfated GAG chains interact more or less specifically with consensus sequences in proteins containing basic amino acid cluster (BB X B or BBB XX B) [62]. Other more specific interactions necessitate specific carbohydrate sequences as the one in heparin-antithrombin III interactions [62]. The small and large fibroblast PGs, decorin and versican, use also the above-mentioned two types of interactions: versican contains lectin-like domains as the cartilage PG and decorin appears to interact with fibronectin and collagen through the protein portions [62]. Syndecan, a cell membrane PG, exhibits both types of interactions, to collagen and fibronectin with the HS and CS GAG-chains, membrane anchorage being assured by the core protein. The lymphocyte homing receptor, Hermes or CD44 carrying CS chains is another example. The transmembrane domain of the core protein is involved in the reorganisation of actin filaments. The presence of alternating sequences of lectin-like domains, EGF-like domains and complement regulatory domains in some human receptors also confirms the importance of the backbone proteins in the regulation of cell proliferation and interactions [62]. Another type of interaction of great physiopathological significance is between some PGs and lipoproteins (LDL). These interactions appear to be responsible for the deposition of lipids in the subintima during atherogenesis [73–76].

This short and by far not exhaustive enumeration of some of the recent aspects of PG-research illustrates the considerable progress accomplished since the first characterisation of GAG-chains in CT-extracts by Meyer, Dorfman and others [59,60].

5. STRUCTURAL GLYCOPROTEINS

It became clear in the early sixties that besides 'collagen', 'acid mucopolysaccharides' and elastin there were locally synthesized constituents in CT-extracts which did not fit in any of these families of macromolecules [77]. The first such glycoprotein was isolated from the corneal stroma and its biosynthesis by keratocytes demonstrated by in vitro incorporation experiments [77]. As the amino acid and carbohydrate composition of CT-glycoproteins was similar to plasma glycoproteins and quite distinct from that of the other CT-constituents, and as they appeared to play a 'structural' role in ECM, we proposed to designate them as 'structural glycoproteins' [77]. Since the characterization of a score of such glycoproteins (fibronectin, laminin, nidogen, thrombospondin, fibrillin and others; for a review see [77]) some other designations were proposed such as CT-glycoproteins or nectins. As far as their biological role is concerned several of them were shown to play a crucial role in cell-matrix interactions. The best understood example is fibronectin. Its structure is known both from protein chemical studies and from gene sequencing [78–81]. Here again alternative splicing was shown by Hynes's and Barralle's teams to produce a variety of isoforms recognized by specific monoclonal antibodies. Some of these isoforms are sequentially produced during development and also in some pathological conditions. Fibronectin was shown to interact with specific cell membrane receptors (integrins) through a limited sequence of amino acids: Arg-Gly-Asp or R-G-D. Ruoslahti's team identified this critical sequence in a number of proteins, some of them, but not all can interact with integrins [82,83]. These adhesion receptors consist of an α and a β subunit, several types of each of them are known. They were shown to be involved in a score of important recognition phenomena such as, for instance, between platelets and fibrinogen, thrombin, collagen and other agonists [82–84] with leucocytes and endothelial cells [85], endothelial cells and von Willebrand factor and others [82–85]. The α chain consisting of S–S bound heavy and light subunits is specific to the ligand, the β subunit is common for several ligands. Not all α subunits are then proteolytically processed to heavy and light chains, but all seem to share some common features, such as calmodulin-like cation binding sequences on the extracellular domain. Some α chains contain a 180 amino acid insertion homologous with a domain in several collagen binding proteins [86,87]. The β subunits have an extracellular cysteine-rich domain and an intracellular tyrosine-phosphorylation site. The non-covalent interaction between the α and β subunits is strengthened by divalent cations. The cytoplasmic domain of in-

tegrins interacts with the cytoskeleton specifically with talin and fibulin [87]. They are therefore capable of transmitting signals from the extracellular matrix to the interior of the cell. At least eleven α subunits can combine with seven β subunits to yield at least 16 heterodimers and these numbers are still increasing.

The Leu Cam leucocyte receptors also belong to this superfamily and mediate adhesion of polymorphonuclears, monocytes and lymphocytes to each other and to a complement component, C3bi [84]. The very late antigen (VLA) family of lymphocyte receptors has also been shown to be part of the integrin family [88]. The deletion or deficiency of a subunit of such receptors can be the origin of severe pathological conditions, as, for instance, the deficiency in Glanzman's thrombasthenia of the GP IIb/IIIa receptor of platelets [89].

There is increasing evidence for an important role of cytoadhesins in developmental phenomena: the position-specific (PS) antigens of *Drosophila* are integrins [90] and R-G-D peptides were shown to inhibit gastrulation [91]. Mutants of both α and β subunits could be related to observed developmental and behavioral anomalies in *Drosophila* [90]. The cell adhesion molecules ICAM-1 and ICAM-2 were shown to act as counter receptors for LFA-1 (or CD11/CD18), a leucocyte receptor. Integrin expression and its up- and down-regulation vary with cell type, developmental and experimental conditions. The phosphorylation of the receptor appears to decrease its interactions both with its ligand and the cytoskeleton [87]. TGFβ enhances the expression of several integrins and can change their specific expression [92]. These few examples clearly illustrate the ever-increasing complexity and biological importance of the integrin family.

Much less is as yet known on receptors recognizing sequences other than the RGD-type, although evidence is accumulating in favor of their importance. Interaction between fibroblasts and elastin fibers or peptides could not be inhibited with RGD-peptides [93]. Laminin and other matrix glycoproteins also were shown to contain other recognition sequences [94]. It appears therefore that for some time at least matrix-recognizing cell membrane receptors will remain in the forefront of ECM biochemistry.

Another important aspect is the transmission of the signal from the activated receptor to the cell interior. Cell-elastin interaction was shown recently to be mediated through the G-protein-phospholipase-C-IP_3-DAG-PKC-pathway [55,56,93].

6. DISCUSSION - CONCLUSIONS

This rapid survey of the already considerable domain of biochemistry and cell biology of ECM can only indicate the amount of detailed knowledge recently accumulated and the manifold directions of research and applications. We can try to summarize these many aspects of ongoing research and speculation in a scheme (Fig. 2) we like to call the 'central dogma of matrix biology'.

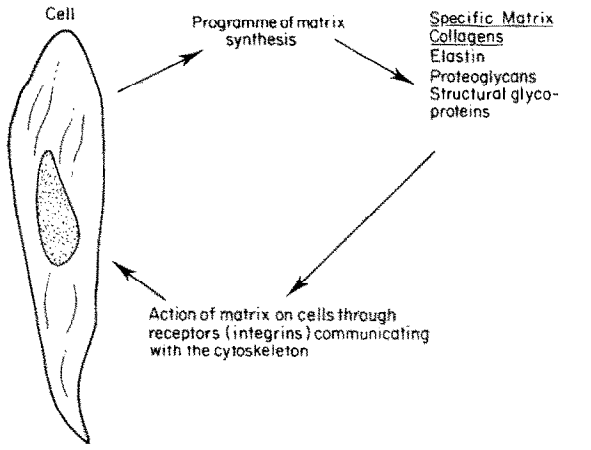

Fig. 2. The informational feedback loop between the cell which synthesizes its specific ECM and the action of the matrix on the cell, mediated through the nectins and the cell membrane receptors (integrins) which communicates 'messages' coming from the matrix to the cell.

This figure illustrates an informational feedback loop which starts with the (developementally regulated) genetically 'programmed' expression of genes coding for matrix macromolecules. This program is characteristic of the state of differentiation of the cell and varies with space and time (aging effects). It has qualitative components: the choice by the cell of genes which will be expressed and a quantitative component – their up- and down-regulation in time and space. Epigenetic factors will then determine the structural organization of the cell- and tissue-specific ECM. This matrix recontacts the cells through the transmembrane receptors (integrins) and mediates the transmission of the matrix-born messages to the interior of the cells. Thereby modifications of the matrix (due to a modified program of biosynthesis or by external factors, inflammation, lytic enzymes, ...) can modify cell behavior. In this way the informational feedback loop may become a vicious circle, possibly involved in the genesis of diseases characterized by modifications of the ECM. Diabetes, arteriosclerosis, osteoarthritis, age-dependent changes are some examples for these type of derangements.

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