Kurt Mosetter, MD

The Structural Dynamics of Fasciae and Muscles

This section will present the "ground substance" or the biochemistry of the extracellular matrix and its dynamic signaling and communicative behavior. Daraus begründen sich hervorragende Möglichkeiten der Therapie und Regulation.-

The Intercellular Substance/Ground Substance

The discovery of cells and their internal life around four hundred years ago was a milestone in the history of modern Western medicine. Cellular mechanisms, the activities of the cellular nucleus, and the details of genetics have gradually become known with ever-greater precision.

However, for a long time, the extracellular space between the cells – the intercellular substance – was relegated to the background and a shadowy existence. This space and its milieu are existential requirements for life with respect to nutrition, control, signaling activity, and the basic nature of cellular processes, both physiological and pathological. Thus, extracellular processes affect and control the cells themselves through contact with the cell surface, ligands, and biochemical pacemaker processes. The intercellular substance is a critical element for understanding bacterial and viral infections, the pathways of carcinogenesis and metastasis, inflammatory processes, and neurodegenerative changes. Beginning from the earliest developmental stages of the central nervous system, structures of the extracellular matrix are essential for maturation, growth, migration, and cell control, differentiation of neurons and glial cells, and organization of the connective tissues and fasciae.

The Ground Substance
(Synonyms: intercellular substance, extracellular matrix)

Composition:

Glycosaminoglycans, proteoglycans, messenger substances, cytokines, myoblasts, fibroblasts, glial cells, osteoblasts, collagen, elastin

Properties:

Viscoelastic network

Functions:

• Pressure-tension-stretch-perceptual network
• Tensegrity-shock absorption system
* Communication and Signaling system
* Transport system
* Factory for replenishing all cell lines

In addition, the activity and complex regulatory functions of nerve cell growth factors, target-region dependent growth factors, and growth factors for collagen

would not be possible without the fundamental functions of the substances located in the extracellular matrix.

Special Features of the Extracellular Space

The extracellular matrix is made up of a jelly-like substance that holds cells together and provides pathways to individual cells for the diffusion and transport of nutrients, signal carriers, oxygen, and messenger substances. The extracellular matrix is also referred to as the intercellular substance or ground substance, and consists of an interwoven network of proteoglycans (PG) and glycosaminoglycans (GAG). These specifically include heteropolysaccharides and fiber proteins such as collagen, elastin, fibronectin, syndecans, and the glycocalyx. The heteropolysaccharides are known as glycosaminoglycans, and are composed of recurrent disaccharide units consisting of the monosaccharides N-acetylglucosamine or N-acetylgalactosamine bound to a carboxylic acid such as D-glucuronic acid or L-iduronic acid. Glycosaminoglycans are esterified with sulfate at the hydroxyl groups (-OH) of their amino sugar, and thus, very high negative charges develop in their side chains from the combination of sulfate and carboxylate groups.

To minimize repulsive forces between neighboring charged groups, these molecules assume a long, strung out conformation in solution. The characteristic distribution of sulfated and non-sulfated sugar residues in glycosaminoglycans offers a specific recognition pattern for a large number of protein ligands that are ionically bound to these molecules. Their binding, communication, and interactive behavior is also influenced by this distribution. In combination with extracellular proteins they form proteoglycans. Typical examples of glycosaminoglycans include hyaluronic acids or hyaluronidase, which serves as a lubricant in joint synovial fluid. In addition, their interactions with the extracellular matrix assure tensile strength and elasticity in cartilage, tendons, and connective tissue.

Chondroitin sulfate is responsible for the tensile strength of cartilage, tendons, and connective tissue. Dermatan sulfate assures the suppleness of skin, vessels, and heart valves. Keratin sulfate is found in cartilage and bone as well as the cornea and the nails. The anticoagulant heparin sulfate or heparin is of particular importance, and has the greatest negative charge density. This substance is produced by mast cells in the extracellular matrix and released into the bloodstream, where it inhibits clotting in electrostatic interaction by binding with antithrombin III. In the extracellular matrix, the network of proteoglycans and glycosaminoglycans mature to become a functional series of small molecular cytokines, growth factors and chemokines. They reside in the extracellular matrix and contribute to its spatial quaternary structure while also serving as a standby reservoir in the proteoglycan receptors of syndecans.

These structures assure super-fast extracellular information processing along with fine regulation of the extracellular matrix with autocrine, paracrine, juxtacrine, and endocrine control of cell response. Through surface recognition structures, receptor binding activity, cell adhesion processes, targeting, and cell-cell interactions, bio-chemical and electromagnetic processes in the extracellular matrix also determine extracellular matrix cell migration and immune response behavior, nerve cell growth, detoxification, and clotting processes. The glycosaminoglycan component typically accounts for (in terms of mass) the largest fraction of proteoglycan molecules, dominates the structure, and is often the principal site of biological activity. In many cases, the biological activity consists of creating a large number of binding sites, which

offer extensive opportunities for the formation of hydrogen bonds and electrostatic interactions with other proteins on the cellular surface or the extracellular matrix.

In addition, there are glycoproteins and glycolipids located in the extracellular matrix and on the external surface of the plasma membranes. These substances are also found inside lysosomal cells, secretory granules, the endoplasmic reticulum, and the Golgi apparatus. Complex oligosaccharides bound to proteins are extremely diverse and highly specific in their recognition and binding activities. Glycolipids in the cell membrane function similarly as highly specific contact and signaling sites for carbohydrate-binding proteins and receptors. Moreover, the extracellular matrix also contains core proteins with covalently bonded glycosaminoglycans.

"Together, the extracellular matrix and cells form a viscoelastic system, which maintains a self-stabilizing structure when impacted by external forces ('tensegrity'). Therefore, the extracellular matrix represents an attractor for all external and internally acting forces similar to a coupled spring, whereby small causes can have very large effects."[1]

The attachment points are typically serine residues. In addition to the proteoglycans secreted in components of the extracellular network, several of these compounds work as integral ECM cell-bridging membrane proteins. Transmembrane domains are thus controlled by extracellular domains, regulated by extracellular ligands, and altered with respect to their biological activity in terms of three-dimensional shape, receptor specificity, and cell surface recognition sequences. Matrix proteins have distinct domains for reciprocal binding, and the same is true for the plasma membrane protein family of integrins. Integrins organize signal transmission between the interior of cells and the ECM. The resulting interactive effects between cellular and extracellular molecules assure a differentiated and milieu-specific flow of essential information in both directions in the service of cell migration and development and the growth of respective types of tissues. The families of lectins and selectins also participate in this process.

Matrix proteoglycans are critical elements for the cellular response to certain extracellular growth factors. For example, fibroblast growth factor (FGF) – an extracellular protein signal that stimulates cell division – initially binds to heparin sulfate components of the syndecan molecules in the target cell's plasma membrane. Syndecan then "presents" the FGF to the specific FGF plasma membrane receptor, and only then can FGF effectively interact with its receptor to initiate cell division.

The ECM is also populated by the interferon and interleukin cytokine families. Hidden and "sleeping" within this ground substance are myoblasts, fibroblasts, glial cells, chondroblasts, osteoblasts, and mast cells, all of them activated, transported and regulated according to need. There is a complex balance between situationally directed tissue restructuring in inflammation, apoptosis, and growth. The principles of equilibrium in the ECM can be beautifully demonstrated on the one side by potent inflammatory substances including tumor necrosis factor alpha (TNF alpha), interferon gamma (IFN gamma), and the interleukins (IL 1, 2, 4, 5, 6, and 12), and on the other side, growth factors, including transforming growth factor beta (TGF beta) and nerve growth factor (NGF). In this setting, pro-inflammatory messenger substances

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[1] Heinrich, H. (2005). Die extrazelluläre Matrix als Attraktor für Verschlackungsphänomene. [The extracellular matrix as an attractor for slagging phenomena] *Ärztezeitschrift für Naturheilverfahren*

such as prostaglandins, histamine, proteases, leukotrienes, along with proteolytic enzymes such as serine, metalloproteinases and collagen protease typically function as rapid responses to emergency situations, which subsequently return to baseline to be replaced by anabolic processes. It is only when these processes are derailed by chronic stress and its metabolic equivalents that they become persistently activated and pathological. Thus, the ECM takes on importance as a key factor for understanding a wide range of disease states.

So elements of the extracellular matrix serve to direct intracellular processes.

Metabolic stress results in energy deficiency and disturbances in energy utilization in muscle and brain metabolism. Over time, it has been demonstrated that along with the pH level in the ECM, the intracellular pH level and the cytoplasmic redox potential shifts toward acidosis in the cellular milieu.

In the stress response there is increased formation of oxygen radicals and activation of the pro-inflammatory scenario that involves TNFα, acute phase proteins, and a series of disparate, synchronous changes such as disturbances in glucose utilization, insulin resistance, hyperlipidemia, AGEs, and lability of the clotting system.

The Extracellular Matrix and Signal Control

The interaction of cells and their surface structures with components of the extracellular space has a profound impact on the development and behavior of individual cells.

Signals related to mechanical stress and associated burdens from the outside shape the living world of this ground substance. Depending on the nature of the signals, very different forms and types of connective tissue can be synthesized. Depending on use and activation, these signals will induce production of collagen and elastin or the synthesis of myofibroblasts. Even those structures that appear more solid and self-contained such as bones and joints are thus highly dependent on function at the cellular level. And even in the context of severe developmental restrictions and dysplasia, they remain shapeable and modifiable well into advanced age.

The form, development, growth, polarization, movement, and at times the nature of individual cells and their functions typically reflect corresponding shifts in the cellular environment.

Interactions and water binding between glycosaminoglycans and proteoglycans also generate fluctuations in charge and electrical and chemical gradients, which open information bridges and transport pathways. This mobility of the ground substance helps maintain the proper organization of connective tissues, fasciae, the cytoskeleton, and biochemical communication cascades.

Key players in extra-intra-inter cellular communication between cells and their microenvironment include the integrin families. Integrins connect structures of the cytoskeleton within the cell through two trans-membrane domains that extend across the membrane and bind the outward-turned external cell surface to extracellular substances. They take hold of the divalent cations of the ECM across an alpha subunit-binding site and by means of their terminal regions in the extracellular space, they are able to bind matrix proteins, cell adhesion molecules, and extracellular ligands. This process creates bridges and guiderails made of laminins, fibronectin, collagen, and a series of glycans (glycosaminoglycans and proteoglycans). In the cytosol, integrins, which have no enzymatic activity of their own, bind to actin and α-actinin

pieces of the cytoskeleton via the adapter proteins vinculin and talin. These fundamental key and nodal points between extracellular and intracellular structures are known as focal adhesion (FA) sites.

Focal adhesion sites are the switch-points for integrin-mediated signal cascades. As integrin binds to extracellular components, this activates and auto-phosphorylates focal adhesion kinase (FAK), which binds across SH-2 domains with cytosolic src kinases and finally, after forming a bridge with Grb2-SH3 domains, activates Ras kinase. This process triggers the more familiar MAP kinase pathway with mitogenic effects on the cell nucleus and sustained gene expression patterns.

Thus, integrins serve as multidirectional messengers. They direct change signals from the extracellular space to the intracellular and intra-nuclear space but also from the cell interior in an outward direction. Depending on the signal state, integrins can modify and structurally influence the cell's docking behavior to components of the extracellular matrix.

Thus, the extracellular space plays a superordinate part in all of the processes and events described up to this point.

The Body's "Semiconductor Chips"

Supersensitive Perception and Superfast Information Transfer

In addition to its many other activities and vital functions, the extracellular matrix also plays another key role.

The extracellular space or intercellular substance provides the human body with an extensive and multiply interconnected and fine-tuned perceptual, communicative, and information network. Electrical potentials are generated by charge distributions along the various long chains and interconnections of branched glycosaminoglycans and proteoglycans. Differential charge gradients can develop depending on the shape, configuration and conformation of the sugar-protein-sugar molecules. Depending on the pressure and tensile forces in the glycosaminoglycan grid, shifts and changes occur in charge, electricity, pH levels, and field strengths. The configuration of geometrical angles and structural patterns within the gel-like intercellular substance is expressed in the form of fluid crystal variations with additional electricity. The form of electricity generated within these grid-like structures is called piezoelectricity. The energy flows and charge gradients vary depending on the geometrical patterns.

Analogous to modern microchips in computer technology, which are information carriers and rapid semiconductors based on silicon and quartz crystals, the extremely finely interconnected and ubiquitously distributed network of the ECM may be regarded as a sensor system, an energy storage device, an information carrier, and a super-fast guidance system.

Water molecules are an important component of this network system, with their specific lattice structures, their interconnections through hydrogen bonds, and their bridge formations with ions and minerals. Minerals such as magnesium, manganese, copper, iron, and zinc always act in their ionic-colloidal form within the gel-like network of charges; in fact, this is the only form in which they generally can be utilized by the body. In this context, metal transporters such as transferrin also act as messenger substances in the ECM. Bonds and bridges with glycoproteins, glycoli-

pids, transmembrane glycosaminoglycans, and integrins modulate the shifts of charges and tension gradients and the resultant electric currents. Each individual component can be configured according to need and the prevailing pressure and tractile forces and the structure can be extensively adapted through charge distribution and chemical gradients. Even the major families of growth factors and cytokines are activated and controlled through such gradients, and directed in their migration.

Parallel electromagnetic fields function as attractors and order parameters within the electrical potentials and streams. These electromagnetic fields constitute a fine-tuned sensory apparatus, an information storage system, and a flexible online communication system. Different levels of energy, electricity, charge, pressure and tractile forces regulate the preferential absorption, amplification, modulation, transformation, and transmission of different wavelengths. This information network is further synchronized by vast numbers of embedded interstitial receptors, free nerve endings, and ramifications of the autonomic nervous system. Interoception and our sense of self are thus based to a large extent on the intercellular matrix.

Charge patterns, electricity, geometrical configuration, pressure and tractile forces are correlated with specific rhythms of frequency patterns.

In this respect, water molecules represent the geometric structural pattern of a tetrahedron. With their fluid crystalline structure, they have specific energy and wavelengths. Arranged in groups, they form clusters with hydrogen bonds; specific fluid crystal forms are created including the icosahedrons found in the tensegrity model. Wavelengths, frequencies, and energy potentials can be modulated through geometrical variation. This can result in the generation of harmonic, resonant energy patterns or dissonant chaotic patterns depending on the energy, charge, and wavelength.

These patterns can be altered by quanta of pressure, weak electrical currents, ultrasound, and especially by means of specific vibration.

Die Muskelvibration als Grundlage der ZRT-Matrixtherapie

“Die biomechanische Stimulation (BMS), als Modul der ZRT-Matrixtherapie wirkt gezielt auf die Stoffwechseldynamik in der extrazellulären Matrix ein. Im Wirkungsbereich der Rehabilitation wird die BMS-Therapie seit Jahren vor allem bei muskuloskelettalen Beschwerden zum Einsatz gebracht. Dieser Therapie liegt das Wirkprinzip der natürlichen Muskelvibration zu Grunde. Auch in völliger Ruhe bewirken abwechselnde Kontraktionen von etwa 2 – 3 % der anteiligen Muskelfasern eines Muskels eine Mikrovibration. Es gibt keinen „Ruhetonus“: In jedem Muskel finden ständig rhythmisch alternierende Kontraktionen statt. Bei Bedarf, wie z.B. in der Kälte, bei Kraftanstrengungen oder beim Schüttelfrost vor dem Fieberanstieg, kommt es zur Frequenz- und Amplitudensteigerung, sodass das Zittern als Zeichen der Aktivierung der Mikrozirkulation sichtbar wird. Die Anregung der Mikrozirkulation im EZM erfolgt durch das mechanische Auspressen der beginnenden venösen und lymphatischen Kapillare. Durch die Kontraktion der Muskelfasern kommt es dabei zum Zusammendrücken der Kapillare mit anschließender elastischer Rückstellung. Durch diesen Druck- und Saugeffekt wird die Mikrozirkulation aktiviert. Dadurch werden Stoffwechselendprodukte, Toxine oder Zellzerfallsprodukte abtransportiert. Diese muskelgetriebene Mikrozirkulation stellt mithilfe einer intakten und durchlässigen EZM die Versorgung aller Zellen im Gewebe sicher.

Die biomechanische Stimulation als Modul der ZRT-Matrixtherapie: Nun bietet sich in der Physiotherapiepraxis und in der sportmedizinischen Praxis mit der ZRT-

Matrixtherapie ein weiteres wirksames Verfahren an, das die Mikrozirkulation im Extrazellularraum unterstützt. Die muskuläre Rhythmik kann von außen durch einen geeigneten Schwingungseintrag nachgeahmt und angekurbelt werden. Von allen energetisch offenen Systemen ist bekannt (Prigogine 1987), dass die Eigenfrequenz eines schwingungsfähigen Systems (Muskulatur) sich an die Schwingung eines äußeren Erregers anpasst oder dessen Rhythmik übernimmt. Diese mechanischen Schwingungen müssen dabei mit den biologischen Schwingungsmustern der Muskulatur übereinstimmen. Biologisches Frequenzfenster von 8 Hz bis 30 Hz und Amplitudenfenster von 0,1 bis 5 mm müssen eingehalten werden. Der Schwingungseintrag erfolgt in Längsrichtung der Muskulatur. Die körpereigene muskuläre „Pumpwirkung", die die Mikrozirkulation wieder aktiviert, wird bei der biomechanischen Stimulation (ZRT- Matrixtherapie) mit speziellen Therapiegeräten imitiert und von außen angestoßen. Dieses Therapieverfahren ermöglicht die Lockerung der Muskulatur durch die Normalisierung des Zellstoffwechsels. Die Physiotherapie wirkt mithilfe der biomechanischen Stimulation (BMS) auf Rhythmik, Mikrozirkulation und Zellstoffwechsel - den physiologischen Bausteinen der Regeneration. Dies unterscheidet die BMS von vielen therapeutischen Maßnahmen in der Physiotherapie, die auf dem einfachen Reiz-Reaktions-Prinzip beruhen. Die BMS muss dringend von vielen herkömmlichen Vibrationsanwendungen abgegrenzt werden, die oft senkrecht zur Muskulatur auf das Gewebe einwirken und mit Frequenzen arbeiten, die in einem Bereich weit über die obere biologische Frequenzgrenze von 30 Hz hinausgehen."[2]

Appendix

What does physics teach us about these phenomena?

The atomic physicist and Nobel prizewinner Dr. Carlo Rubbia was the discoverer of the ratio of form-giving energy to material particles in what is known as the mathematically calculable natural constant. Approximately 1 billion energy units (one to 9,746 times 10^{108}) are required to create one particle of matter. Formative effective forces include quanta of pressure, charges, electrical potentials, electromagnetic fields as well as biophotons and light.

Light imparts its effects through wavelengths and through specific light-sensitive ion channel receptors. Scientists in the field of optogenetics have shown that there are actually "light switches" in the brain that can be measured and activated. Light can influence or control electrical excitability, the cell membrane potential, pH value conditions, and the influx or outflow of ions through their channels. Light can be absorbed by clear crystals and split in such a way as to generate the colors of the rainbow from white light.

Charge patterns, chemical gradients, liquid crystal structure, and piezoelectric currents within the ECM are systematically interwoven with the cytoskeleton, the cell membrane, and the intracellular structures. Depending on the nature of the external signals, all required growth factors, messenger substances, and cell lines can be synthesized in the extracellular space. The maturational processes, normal cell migration, cell growth and the production of the respective glycoproteins, glycosaminogly-

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[2] Dickreiter, B. / Fröhlich, T. (2013). ZRT - Matrixtherapie. Zellbiologische Regeneration beim Leistungssportler. *medicalsports network*. 2. 40-43.

can and proteoglycan, are all regulated within the communication network of the ECM.

Several glycosaminoglycans are anchored and interwoven in the cytoskeleton. In their charge-dependent binding patterns, collagen, elastin, laminins, alpha dystroglycan, and dystrophin all form bridges to and within the cytoskeleton. Filamins, alpha actinin, vinculin, paxillin, and talin are anchors to which the glycosaminoglycans from the cytoskeleton can dock. The geometric pattern, piezoelectric potentials, and the organizational patterns within the fluid crystalline structure thus play a key role in the construction and functioning of the cytoskeleton.

Membrane-bound proteoglycans such as syndecan and beta glycan are involved in the normal configuration of the cytoskeleton, in cell adhesion, and in the synchronization of binding activity of FGF and TGF.

Basal membrane proteoglycans such as agrin are responsible for the aggregation of acetylcholine receptor complexes. Perlican functions as a filter – or filtration barrier – for all materials in the intra and extracellular space. Aggrecan provides the key material for hyaluronic acid, chondrocytes, cartilage, and a hydrated joint gel. As part of its anchoring function, versican helps fine-tune pressure and tension forces between the ECM and the cytoskeleton.

A family of leucine-rich proteoglycans is responsible for binding collagen and related fibril formations.

‘Cell adhesion’ proteins function as bridges from the interior of the cell to the outside extracellular space. These protein families are also charged and involved in maintaining homeostasis, electrical tension patterns, chemical gradients, and electromagnetic field potentials.

Major members of this group include the integrins, selectins, cadherins and the immunoglobulin families.

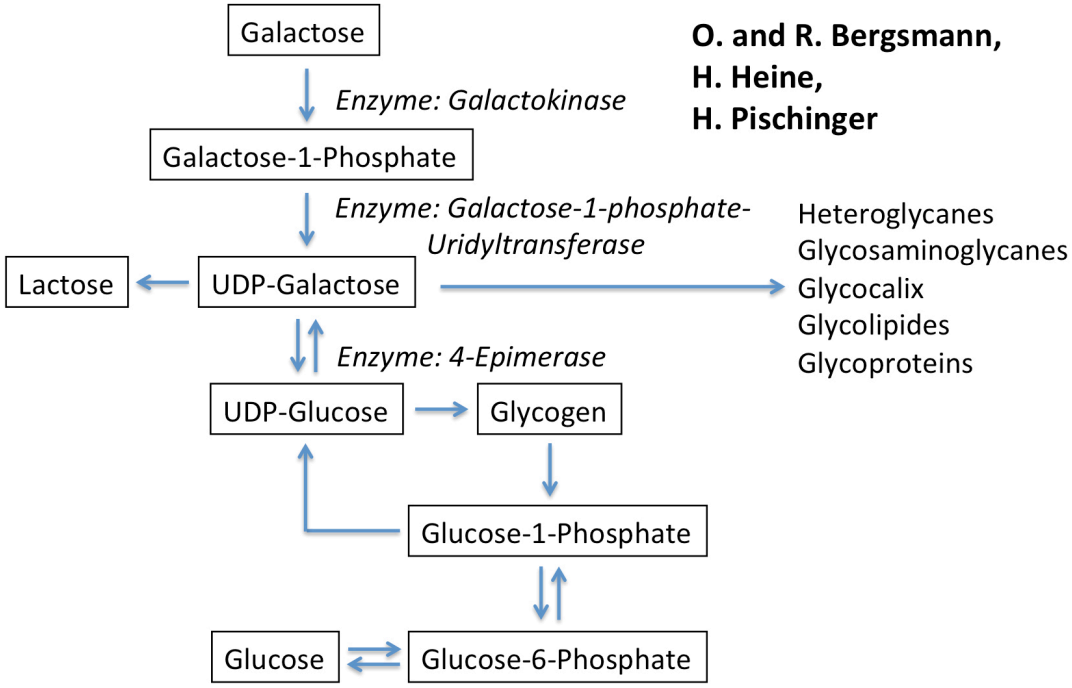
Donald E Ingber is the scientist most responsible for the basic research on the organizational structure and function of the cytoskeleton based on the principles of tensegrity.

The economic construction and maintenance of the cytoskeleton in a maximally harmonious geometric vector model is inextricably linked to the structural laws governing the system of the ECM.

Synthetic Pathways for Components of the ECM

All of the synthetic pathways for glycosaminoglycans and proteoglycans as well as the heteroglycan group depend upon galactose. The synthesis of GAGs and PGs and heteroglycans is characterized by a specific metabolic biochemical pathway. The key substance galactose and its biochemistry have been researched in detail and are documented in major academic textbooks.

The biochemical metabolic pathway for galactose shows how galactose, as the terminal component of all heteroglycans, represents the substrate for biosynthesis and is a metabolic anchor in cells and the intercellular space.



The Biochemistry of Galactose and the ECM

With the processes of glycosylation, the synthetic metabolic pathway toward the glycosaminoglycans also represents a critical biochemical genetic regulatory mechanism for what is known as post-translational modification. This process involves large numbers of essential substrates, hormones, enzymes, messenger substances, receptors, and life-sustaining components of the intra and extracellular space. Together with the signal communication and cell recognition sugar sialic acid (N-acetylneuraminic acid), galactose plays an vital role in cell adhesion, cell signal cascades, immune regulation, neuroregeneration, and neurobiochemical processes.