EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Coden USA: EJBPBO
Volume: 13
Issue: 9
Year: 2026

THE CELLULAR GLYCOCALYX AND ITS BIOPHYSICAL AND BIOMOLECULAR BEHAVIOURAL ASPECTS

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How to cite this Article: Y. K. Lahir. (2026). The Cellular Glycocalyx and Its Biophysical and Biomolecular Behavioural Aspects. European Journal of Biomedical and Pharmaceutical Sciences, 13(9), 51–72.

Article Received on 05/08/2026 **Article Revised on 25/08/2026** **Article Published on 01/09/2026**

ABSTRACT

Biological cell is a basic dynamic structural and functional entity of a living being. Their molecular make-up exhibits varied physicochemical and molecular functional complexities. These lead to the effective manipulation of their overall behaviour and ensure their survival in stressful living conditions. Such conditions include invasion of pathogens, toxins and most of the physiological disorders and make efforts to ensure its sustainability. Glycocalyx, cell membrane, cytoskeleton along with cell organelles are the participants in this adaptive pursuit. Although innumerable investigations are reported but still there exists many lacunae in the various functional mechanisms. As one dives deeper in the subject to get the tunnel view of these processes, one encounters numbers of doubts. It seems to be important to have better understanding of the intricacy of dynamic regulations of a cell with respect to its reorientation, sensing the stimuli, transduction of physical and biochemical/molecular cues and ability to respond. This presentation is an effort to understand the functional effectiveness of glycocalyx during various physiological and some common pathological conditions.

KEYWORDS: Agranulocytes; chondrocyte; dendritic cells; efferocytosis; excitation-contraction coupling; flippase enzyme; glycocalyx; glycosylation; granulocytes; immune cells; mechanical signal transduction; muscular fatigue; myocytes; natural killer cells; nerve cell; phosphatidylserine; Shedding of glycocalyx; skeletal muscles (striated and smooth muscles fibers.

Overall concept

Physiologically normal behaviour on the part of cell is the result of suitable morphological, molecular, and biochemical homeostasis of a cell in its ambient environment. Cellular morphology is maintained due to the structural aspects like functional glycocalyx, cell membrane, cytoskeleton and proportionately sized and structured cell organelles. These components ensure specific shape, size and other physical parameters like elasticity, plasticity, viscoelastic nature.[1] The functional aspects depend on the biochemical constituent, their conformation of the participating biomolecules. A perfect or most suitable cellular behaviour in bioentities ensure its appropriate functions and survival. The structural and functional aspects are synchronized based on its cytohistology, cellular, molecular and cell-physiology during normal and pathogenesis. Structural and functional unit i.e., a biological cell (unicellular as well as multicellular organisms) plays very effective role during its life span. There are various functional modulations in an organism under various pathological conditions and their mechanism involved should be well understood in order to secure the remedial process. Inflammation appears to be the initial stage of most of the pathogenesis.

Generally, there is an overall degradation along with structural and functional impairment of glycocalyx and vascular functionality on the onset of inflammation. The glycocalyx is the most peripheral component of a cell and it is the first target of any invasion or physiological alteration. The glycocalyx is present on the luminal surface as the most peripheral lining of a cells. From biomolecular point, it consists of complex-polysaccharide-proteins. Any physical, chemical and physiological cues for pathogenesis developed in the

ambient extracellular matrix (ECM) impacts this layer of the cell. On the onset of inflammation, the vascular cells and endothelial cells face the invaders or any type of agent causing inflammation. The glycocalyx job is to modulate the process of inflammation; it also disrupts the cyclic process of endothelium dysfunction during inflammation. It facilitates the site of inflammation as a potential ground for the success of remedial and therapeutic strategies.[1] As far as bulk of glycocalyx is concerned, it is composed of glycoproteins, glycosaminoglycans (GAGs) (proteoglycans), and proteoglycans. Most of the glycans are present in abundance as a free of protein and lipid components. It exhibits different types of complexes of sugars, like glucose, galactose, mannose, N-acetylneuraminic acid, N-acetylglucosamine, N-acetyl-galactosamine, glucuronic acid, xylose and fucose.[2,3,4] The complex structural aspect of glycocalyx ensures various functionalities of various modes and these modes affect the behaviours are with respect to the external cues/stimuli.[4] Although glycocalyx is present in prokaryotic and eukaryotic cells but there are differences between the two; as mention in following table.

TYPES OF GLYCOCALYX IN PROKARYOTES

THERE EXISTS TWO TYPES OF GLYCOCALYX AMONG BIOSYSTEMS. EACH DIFFERS IN THEIR ORGANIZATION, ATTACHMENT AND PROTECTIONAL ASPECTS.

GLYCOCALYX AS SLIME(capsule like) LAYER	GLYCOCLAYX AS CAPSULE (SOFT BRUSH LIKE LAYER
i- It is slime coat which is unorganized, attached loosely to cell membrane. It consists of glycoproteins, and polysaccharides. Mostly, it is present on the cell surface of bacteria. ii- It acts as a protective cover against dehydration and prevents loss of nutrients. iii-It helps in the formation of biofilms around the bacteria. This biofilm lodges communities of bacteria that adhere to the surface . iv-This capsular structure can be readily separated, thus; it is not a strong protective cover. v- It facilitates survival of bacteria in different ambient environments; e g., slime layer of *Vibrio cholerae* ; The slime layer helps in its attachment to the lining of intestine.	i-This capsular layer is highly organized and attaches firmly around the bacterial cell wall. ii-It is sticky layer with gummy consistency. iii-It is sturdy and provides strong protection to the external threats from immune stimuli and helps to avoid phagocytosis. iv- This capsular layer facilitates surface adhesion and the tissues of host and results in pathogenetic bacterial, e.g., *Bacillus anthracis.* Their capsule is rich in amino acids that are pathogenic causing diseases; *Streptococcus pneumoniae,* these target immune cells during immune interactions.

GLYCOCALYX AMOMG VARIOUS MAMMALIAN CELLS

Glycocalyx of erythrocytes

Erythrocytes have well developed glycocalyx and primarily consists of glycoproteins and glycolipids. This repairable layer provides protection, regulation of vascular permeability during their journey through blood and body fluids, differentiate 'self-cells' from 'non-self-cells' and perform adhesion as per the need. The glycocalyx also participate during different pathogenic conditions like sepsis, diabetic conditions. It is one of the main parameters that participate in the development of therapeutic practice.[5,6,7,8,9]

Glycocalyx of leucocytes (granulocytes)

It is also named as 'pericellular matrix'. This peripheral layer is made of glycosylated biomolecules securely linked with cell membrane and acts as interface between blood and the leucocytes. The biomolecules (glycoproteins, glycolipids), constituting pericellular matrix are same as that of commonly present in glycocalyx. Basically, the pericellular matrix facilitates the intercellular recognition, communication and intercellular adhesion. This tendency supports the interactions between various cells of the body and also pathogens and organisms that infest and harm the biosystem. This peripheral layer also regulates the interactions between endothelial vascular cells and differentiation between 'self-cells and non-self-cells' and healthy (normal) and defective/diseased cells. It also helps the adhesion molecules and ensure their adhesion and direct the path of cells during formative movements of the specific cell to the formative zones during embryogenesis.[10]

Glycocalyx of Natural Killer cells

The natural killer cells are larger lymphocytes (type of granulocytes) and come under innate immune system. This is because these do not participate in adaptive or antigen-specific immune interactions. These cells do not reorganize their T-cell receptor of immunoglobulin gene from the configuration of their germline.[10] The cells acting as cytolytic effector units and resemble natural killer cells have been taken as a part of innate immune defence system prior to T and B cells; these cells are considered to be more effective. Currently, all three lineages persist in coordination where NK cells are more than B-cells in a ratio of 3 to 1. These cells have 'antigen-specific-memory.' The N K cells exhibit significant role during host defence response and fatal infection in case of children.[10,11,12] Since, these cells are the type of granulocytes and have similar glycocalyx.

The natural killer cells are significant during the onset of cancer and metastasis because these cells give innate immune response. These cells employ activating as well as inhibitory receptors to differentiate 'self-cells' and affected cells (diseased cells). Under normal conditions, they release lytic granules and induce apoptotic receptors, finally kill the infected cells due to virus and tumoral cells. Since, cancer cells exhibit microevolutionary phenomenon; during this process cancer cells avoid identification and then destruction involving innate immune cells. Cancer cells shed NK activating ligands or overexpression of ligand concerning NK cell inhibitory receptors, as a result the cancer cells evade the killing effects of innate immune cells.[13,14,15,16,17,18,19,20,21]

Glycocalyx of agranulocytes

Glycocalyx in agranulocytes is mostly same in location, composition as found in other granulocytes. This cell component actively participates in 'cell-recognition', intercellular communication and intercell adhesion. In case of interactions with endothelial cells, it facilitates the regulation between the endothelial vascular tissue and shape of the erythrocytes as these pass-through capillaries. Any type of disruption to glycocalyx results in pathogenesis.[10]

Glycocalyx of immune cells

The glycocalyx is present as the outermost fluffy biochemical layer. It actively participates in almost all cellular activities and behaviour. It seems very genuine to understand the structural and functional aspects of glycocalyx. It role is very important during normal healthy state and also during diseased state whenever there is invasion of pathogen.

The glycocalyx exhibits specific behaviour during inter cellular interactions. The main components of glycocalyx are glycosaminoglycans (proteoglycans), glycoproteins and glycolipids. There variations in the amount of this composition in different cells. It serves as mechanosensor, protects membrane, retains ligands and cell-to-cell interactions.[22] This peripherally located component of cell helps to identifying healthy cells and differentiate transplanted cells, diseased cells, and invading organisms or pathogens. It plays significant role during cell-cell adhesion and cellular migration during embryonic development. Understandably, it also plays an essential role during functionality of immune cells and therapeutic interactions or manoeuvring.

The glycocalyx is a fluffy dense layer adjacent to the plasma membrane. This is differentiated in to region tightly attached the plasma membrane (inherent part) and an outer region which may be attached to extracellular matrix or may be free (in case of freely moving in body fluids). Biochemically, glycocalyx consists of glycolipids, glycoproteins, oligosachharide and glycoproteins as trans membrane proteins. Transmembrane glycoproteins like selectin-E, selectin-P and selectin-L facilitate the recognition of specific oligosaccharide present on the membrane of the interacting cell or organism. This feature is very useful during adhesive interactions among endothelial cells.[22,23] Such oligosaccharides behave like "cell markers" and help to distinguish between different type of cells. The trans-membrane glycoproteins present on the membranes of endothelial cells and leukocytes interlink with help of fucose, galactose, N-acetylglucosamine and N-acetylneuraminic acid (also called sialic acid). The N-acetylneuraminic acid is commonly present at the terminal end of the cell surface glycan in most of the mammalian cells and it plays functional role in "cell to cell recognition" and modulations during immune responses.[22,23]

Reitsma et al. reported that the endothelial glycocalyx is carbohydrate enriched layer on the endothelial cells in the blood vessels; broadly, it may be considered to be a meshwork consisting of soluble molecules.[24] These molecules are derived from plasma and/or endothelium. Under normal conditions there exists a dynamic balance between the flowing blood and the soluble components of glycocalyx. This equilibrium affects the thickness and the composition of glycocalyx. Based on the nonquantitative studies on glycocalyx is made of proteoglycans, glycosaminoglycan, and glycoproteins. Proteoglycans include syndecans and glypicans, other being mimecan, perlecan, glycolipids and biglycan, these may diffuse in blood stream but reside in glycocalyx. There are five glycosaminoglycans, namely, heparan sulfate, chondroitin sulfate, dermatan sulfate, keratan sulfate, and hyaluronan; these have varied functions. Although glycocalyx covers the boundary of a cell either on all sides or at least their free sides. This biochemical fluffy coat protects, help in intercellular communication (both physical and biochemicals) and also influence the inter-cellular interactions.

Immune cells have a very significant role during infection or onset of pathogenesis. It is important for them to have some of the specific mechanical functionalities, this is more essential for T-cells. Elasticity, plasticity and viscoelastic properties play significant role in the manoeuvring the impacts of pathogenic agents. These cellular aggregates exhibit varying degree of elasticity depending on the stiffness of mesoscale multicellular aggregates and the mechanical response each cell present in the cluster formed. The activation of the immune components of system. On activation the T-cells undergo multicellular aggregation and perform mechanical activities. The immune cells act as 'maker-self-cells'.[3] The sialic acid and sialic acid binding receptors present on the cell membrane are called 'siglecs' (immunoglobulin-type lectins, come under family 1-type lectins). Many cancer cells exhibit membranous 'sialylated proteins and lipids. This over exhibition relates with immune system and reduced the response of the cell or genetic response with respect specific stimuli. This assists the immune cancer cells to

avoid the impacts of immune cells.[3] It is active participant in processes like vascular permeability, inflammation, thrombosis, mechanotransduction, cytokines signalling during normal and pathogenic conditions. To be a participant this layer has to undergo remodelling and heparanase is the prime enzyme to play major role in this process. It splits the chains of heparan-sulfate at the level of proteoglycans present in endothelial glycocalyx and renders it dysfunctional during organ fibrosis, sepsis and viral infection.[25]

Glycocalyx of dendritic cells

The glycocalyx of dendritic cells have similar basic conformation and molecular structure. In all possibilities there are some changes with respect to specific to the functional needs. Dendritic cells participate in transporting antigens from peripheral tissues to lymph nodes vis lymphatic circulation. For this function, the lymphatic endothelial receptor (LYVF-1) involving the respective ligand, the hyaluronan are docked on its surface. An 'antigen carrying/presenting cell, i. e., dendritic cell has to undergo 'immune surveillance'; this step is essential for forming and controlling immune response in a biosystem. It is complex interaction and is accomplished involving a synchronized inter action of specific adhesion receptors, chemicals stimulating cues that can inaugurate transport towards the lymphatic capillaries, later this transit go across the endothelium and the respective barrier.[26,27] This transportation involves the role of specific adhesion receptors, chemical signals, interstitial transportation in the direction of lymphatic vasculature, thereafter move across endothelial barrier while crawling along the inter luminal surface. White blood cell having about 10 µm have to cannot pass through.[26]

Glycocalyx of skeletal muscles (striated and smooth muscles fibers)

The glycocalyx of skeletal muscle is structurally and functionally dynamic in nature. It concerns with mechanical features, efficacy of signaling pathways, functionality of glycocalyx of muscle like muscular contraction and expansion, muscle fatigue, and adaptability. Structural and compositional aspects of glycocalyx of muscle is similar to the glycocalyx of other cells. This fluffy layer is relatively thinner as compare to glycocalyx of other cells. It is rich in sugar compositional molecules (glycoproteins, proteoglycans). These molecules are protective, binding and bring about connection between muscle fibers and ambient matrix. Its molecular components are glycoproteins, glycolipids, proteoglycans and hyaluronan (hyaluronic acid). Glycoproteins, glycolipids, and proteoglycans are the conjugated protein polymer molecules and hyaluronic acid (hyaluronan) is a type of glycosaminoglycan (GAG) (it related to retention of water). Thickness of mesh-like glycocalyx varies in different conditions of physiology, mechanical stress and inflammation, it acts as a molecular barrier and closely associates with extracellular matrix and with cell membrane. The glycocalyx is one of the functional units with respect to selective permeability; for this efficiency the aquaporin channels, membrane proteins like ion-pumps working consuming ATP and the agents that help in evolving electrical potential and action potential. Such components are established so that suitable functional membrane potential is maintained. The glycocalyx invaginates into sarcoplasm and modifies as t-tubules; these play active roles during electrical signaling and muscular contraction.[28,29,30] The glycocalyx is most suitable biological components that provide protection and keep the tissue lubricated. The specific level of lubrication facilitates its functionality. This principle is applicable to smooth muscle fibers. The muscular cells/tissues undergo mechanical stress. These cells/tissues are generally hydrated and have specific viscoelasticity; because of these features these cells and tissues have ability to 'absorb and dissipate forces during its contractile nature'. The glycocalyx maintains the balance of the fluid and osmotic pressure in the muscular cells/tissues. The glycocalyx of muscular cells/tissues have high glycosaminoglycan (GAG); in this type of molecules, particularly, heparan sulfate and hyaluronan are much more and these help in originating and maintaining appropriate osmotic pressure (these molecules attract water molecules and retain it). Thus, play major role in hydration that ensure the functionality of these cells /tissues. (any type of disorder is likely to result in dehydration or edema). The hydration also provides suitable medium for the biochemical interaction that maintain its metabolic status.[31] The glycocalyx of muscular cells/tissue plays very significant role during intercellular and intracellular signalling processes. Cell signalling phenomenon plays basic role of conveying chemotactic messages concerning growth, locomotory and responsive movements, repairing process, The signaling molecules have ability to link growth factors, cytokines, chemokines, and participate the muscles physiology and biochemistry. These cells/tissues have ability to regeneration better and faster in comparison to other type of cells and tissue. The interaction between muscle cells/tissues and glucose is good example to represent the role of glycocalyx, signaling molecules and receptors. The glycocalyx gives response to uptake glucose involving insulin receptors; elevates the rate of uptake of glucose and its metabolism in muscles. Glycocalyx also participates in releasing the inflammatory responses. This response is facilitated the interaction between glycocalyx and selectins.

The glycocalyx of muscle cells/tissues acts as a physiological barrier and regulates the degree of permeability for the endogenous and pathogen, toxins and the factors that act as modulatory agents during inflammation and muscular exercise. Glycocalyx is located on the outer most periphery of cells; it is the first component to form interface with extracellular matrix, molecules, various cells and any external and internal pathogens. So, it is obvious that its interactions with all such agents have to be selective and preventive in order

to maintain physiological and biomolecular homeostasis. The interaction and entry or expulsion of pathogens and biochemicals has to be selective and favorable to the processes like repair, regeneration and physicophysiological balance or homeostasis. The glycocalyx acts as efficient agent to detect sheer stress due to the flow of body fluid and converts these mechanical fluctuations in to respective chemical signal in the form of useful biomolecules. It regulates the contractile mechanism of the muscle cells/tissues (mostly involves protein kinase C (PKC). The functionality of glycocalyx with respect to its **mechanical properties** and **muscular contractability** is directly related. It possesses specific mechanical properties which participate in the transmission of the force and the forces evenly spread and also reduces the strain on each individual muscle fiber. This feature of glycocalyx ensures the stability of the muscle fibers under action.[32,33]

Glycocalyx causes effects on the **calcium ions** which important for muscular contractability. The glycocalyx can change the functioning of Ca^{++} as it causes the change the activity of ion-channels and ion-pumps these functions help to control calcium ions in a biosystem. Thus, glycocalyx influences the up-take and release of Ca^{++}. Basically, calcium concerns with force and speed of contractability of muscle. Glycocalyx participate in the process of **excitation-contraction coupling**: The process of excitation-contraction coupling relates with the electrical signals (also known 'action potential'. The glycocalyx affects the process of the interactions between cell surface receptors and ion-channels, functionality of 'voltage-gated calcium channels which is responsible for calcium up-take by muscle cells.[34]

The moving blood i.e., flowing blood in vessels produces shear-stress on the endothelium and it adds to the ability of barrier for the movements of solute and water across the underling tissue and blood. It also causes changes in the rate of 'permeability to solutes' and the 'hydraulic conductivity'. There is an observable influence of shear-stress on the quality of transport through endothelium during acute and chronic conditions. This impact is seen on individual pathways like tight-junctions, adherence junctions, vesicles and leaky spots which influence the solute movements during acute and chronic conditions and these can be experimented.[34]

Glycocalyx and muscular fatigue

Muscular fatigue is an interim state of muscle, when it loses the ability to generate force or is exhausted to generate force, mostly due to physical exercise and neurological tiredness. During physical or physiological exhaustion, mostly muscles are involved and these do not perform as per normal anticipation. This interim state exhibits extreme weakness, heaviness or dull ache in the physical body and inability to respond to any level of activity. During this phenomenon either particular muscle or group of muscles are affected. This state relates with sudden vigorous exercise, health status, aging and some disorders of nervous system. Muscular fatigue is manifested as 'peripheral fatigue' and 'central fatigue'. Peripheral fatigue involves muscle only and mostly it is due to metabolic discrepancies. Metabolic fluctuations such as accumulation of inorganic phosphate due to the imbalanced break down of ATP, depletion of phosphocreatine and glycogen, accumulation of H^+ ion because of metabolic acidosis and motor neuron disease and also due to muscular dystrophy, cardiovascular issues, cancer, or stroke. Commonly inadequate nutrients or malnutrition, dehydration also exacerbate fatigue. These metabolic conditions affect the contractibility of muscle fibers.

The recovery of peripheral fatigue occurs within short time to longer duration depending on the degree and severity of fatigue.[35]

In central fatigue, there is an involvement of nervous system more so a neuromuscular involvement. Muscular functionality relates with the nerves, brain and spinal cord. They origin from brain, spinal cord and center of nerves that innervate vast variety of muscles. The sleep, mental exhaustion, structural damage, or misuse of drugs used to fight depression, anxiety, severely disturbed mood etc., (mental disorders) are the cause of central fatigue.

Glycocalyx influence the status of hydration and is able to regulate degree of dehydration under normal physiological conditions. The hydrating ability of glycocalyx relates with maintaining the appropriate level of hydration and this is associated with the sugar compositional molecules like glycoproteins, proteoglycans components. These can help to maintain specific degree hydration and help to fight fatigue. Glycocalyx has ability to modulate or exacerbate the degree of inflammation due to its interactions with immune cells and cytokines. Thus, regulates the fatigue severity. Glycocalyx is functionally potent enough to directly or indirectly influence the metabolic homeostasis by regulating transport of metabolites and nutrients through ambient matrix 'into and out' and facilitating the maintenance of energy homeostasis. Triple adaptive roles of glycocalyx play major role in retaining normal glycocalyx and ensure capacity to endure mechanical stress (generate and transmission of forces), promoting metabolic limits and restructuring it. The resistance training and providing mechanical protection to muscles ensure the normal structure and thickness of glycocalyx. The glycocalyx affects the growth and ability to adapt by interacting with growth factor receptors thereby activating signaling cascades and enhancing protein synthesis. It is likely to cure muscular hypertrophy. This fluffy layer modulates the sensitivity for insulin by interacting insulin receptors and regulate up-take of glucose as per the need of muscles.[30,36]

The cardiac muscle (myocytes) possesses a surface coat called glycocalyx

Cardiac glycocalyx is present on the peripheral surface of sarcolemma of individual cardiac muscle cells. Its compositional components are glycoprotein (sugar-protein) and proteoglycan (sugar-lipid) chains. It binds calcium ions and the surface of the cardiac muscle cell; it is not directly needed for baseline slow inward calcium current during contraction. The significance of slow inward calcium current during 'excitation-contraction coupling process' has been highly investigated.[32,33] The current concept of calcium translocation from ambient extracellular medium into the cell or 'sub-sarcolemmal compartment. The surface coat of sarcolemma (glycocalyx) regulates it. The glycocalyx gets devastated in myocytes and can be separated from heart of the adult using a solution of low calcium, collagenase and hyaluronidase. On comparing the 'trabeculae or papillary' muscles, one can conclude that glycocalyx is not necessary for the formation of slow inward calcium current.[34]

Glycocalyx of nerve cell

The basic structure of glycocalyx of nerve cells is similar to the glycocalyx of other cells. Further, it is very similar in composition to the endothelial glycocalyx. Its constituents such as proteoglycans, glycolipids, are also similar. Its inner interface is securely linked with the neurolemma of nerve cell and axon. Over all, the fluffy and soft biomolecular layer performs many biophysical and physiological functions that ensure supply and drainage of suitable molecules that help to maintain its physiological homeostasis. This phenomenon also maintains appropriate functionality of the (cyton) and the axon of the nerve cell. Glycocalyx is an essential developmental component for the developments of nervous tissue.[37] The proteoglycans and syndecans and glypicans are under one heading and constitute core proteins and these link with membrane of the nerve cell. These act as syndecans or glycosylphosphatidylinositol anchor.[38,39,40]

The processes like formation of reactive oxygen species, matrix metalloproteinases and heparanase disturb the stability of glycocalyx. Even 'profibrotic events' and the remedial pharmacological approaches have potential to disturb the stability of glycocalyx.[41] These syndecans include syndecan-1, syndecan-2, syndecan-3, and syndecan-4 and form a family. Syndecan-1 associates with vascular endothelium and binds with (HS), (CS) and keratan sulfate. Syndecan corelates with sheer force for the flow of blood (42-Koo et al. 2013). The members of family glypican consists of glypican-1, glypican-2, glypican-3, glypican-4, glypican-5, glypican-6. Only glypican-1, is associated with endothelium. The branch linkage has (HS).[5,40,43] The proteoglycans (chondroitin sulphate and heparan sulphate) are ubiquitously distributed in the central nervous system and chondroitin sulphate gets diffused in the extracellular matrix and the nerve cells within ambient zone. It is also one of the major constituents of glycocalyx/perineural mesh. Heparan sulphate more linked with the interface between neural, glial cells and the synapses. This heparan sulphate also associates with the peripheral nervous system. Both these constituents have proteins as core which anchors the repeats of disaccharide chains which are sulphated intermittently at specific sites.[44] Non-sulphated hyaluronan (a member of Glycosaminoglycan -GAG) does not possess any charge and does not link with proteins core; but it connects with cell membrane through receptors of CD.[44,45] The negatively charged chains of glycosaminoglycan link with plasma proteins while positively charged chains associate with ion via electric charge effect. The unique structural aspect of such chains gives specific local charge density. The degree of sulphation regulates the binding features and biological impacts of the proteoglycans in glycocalyx.[44]

Glycocalyx of osteocytes

The musculoskeletal set up in an organism includes bone, cartilage, ligaments and tendon. These connective tissues play significant roles as frame-work that maintains structural support, articulation of ligaments, tendon and respective muscles and guidance during the growth of the individual.[46] Osteocytes are located within the very hard matrix full of minerals. This made the investigation very difficult to the extent that researcher paid attention the readily available cell rather than osteocytes. Whatever information could be made available was based on the study of histology of bone. The information about osteocyte, osteoblast and osteoclast was based on the cells procured from the surface of bone. They treated the procured materials with collagenase hydrolytic enzymes and chelation of calcium.[48] The study on cell line to investigate their molecular manipulatory mode of their functions. Osteoblasts can become either osteocytes, form lining of bone and act as ling cells, or face apoptosis. Osteocytes are derived from mature matrix forming osteoblasts which embed in the matrix of the bone. Fairly good amount of collagen surrounds the osteocytes which are likely to be embed. This collagen is the product of their own matrix forming mechanism or by the cells surrounding them. These develop cellular extensions (future dendritic processes) as these descend in the matrix. During descend these extensions finally contact the earlier embedded osteocytes.[48,49] Organic collagen and inorganic hydroxyapatite and of these two the network of collagen adds to strength of bone and retain original strength after fracture but does not change the stiffness of bone. When osteocytes undergo maturation, processes like collagen network, alignment of osteoblast and formation of lacunae also occurs. There exists amicable corelation between equine, ovine, and murine bones and osteoblast along with oriented collagen matrix. The interaction involving matrix and process of osteogenic differentiation and embedding of osteocytes in polarized appropriate environment. When the process of development, tension, compression, and effects of shear forces due to activities of animals play role in the

defining the axes of osteocytes and osteocytes lacunae and the direction of forces. There are interactive communications between extra cellular matrix and osteocytes when there is a mechanical stimulation. The extra cellular matrix components like glycoproteins, hyaluronic acid are set in mesh of glycocalyx. The glycocalyx associate with the osteocyte membrane to 'lacunar cellular system' membrane and functions to sense(detect) and transduce mechanical signals from the extracellular matrix or the fluid flowing to the bone cells.[49] The monomeric heparan sulphate proteoglycan protein Perlecan/Shpg2 help to perform the functions of glycocalyx. The glycocalyx present in pericellular space (ambient space) present in the extracellular matrix play significant role during osteocyte mechanotransduction. Further, the molecules of glycocalyx behave like 'tether' or like ligand to help osteocyte membrane receptors, transmitting mechanical signals caused because of changes of extracellular matrix and impact of shear due to fluid on the surface of osteocytes.[50]

Role of extracellular matrix (pericellular matrix)

The connective tissues are very intactly associated with extracellular matrix. This matrix is made of interdepended fibrous protein like proteoglycans, glycosaminoglycans. These proteins provide 3-dimensional surroundings which is functionally and structurally support the cells present in the vicinity. These cells nurture, grow and differentiate in this proteinaceous ambient environment. This component of the tissue exhibits some disorders either due to genetic origin or acquired physiological nature that affect its structural aspects and the homeostatic aspects resulting in the health issues. There is huge lacuna regarding these aspects and their mechanisms. The extracellular matrix has molecular and physiochemical disoriented architecture offers obstacles during the development and therapeutic options. This is a big issue among other pharmacological difficulties. These conditions are quite common among individual suffering from mechanotransduction and connective tissue diseases,.[51,52,53,54] Most of the components are the products of monosaccharides. These are mostly constructed as a result of translational products of interaction of enzymes known glycosyltransferases in the endoplasmic reticulum and Golgi apparatus. There is no gene action involved. As a result, the glycocalyx composition changes in different types of cells, even its developmental stages.

Glycocalyx of chondrocyte

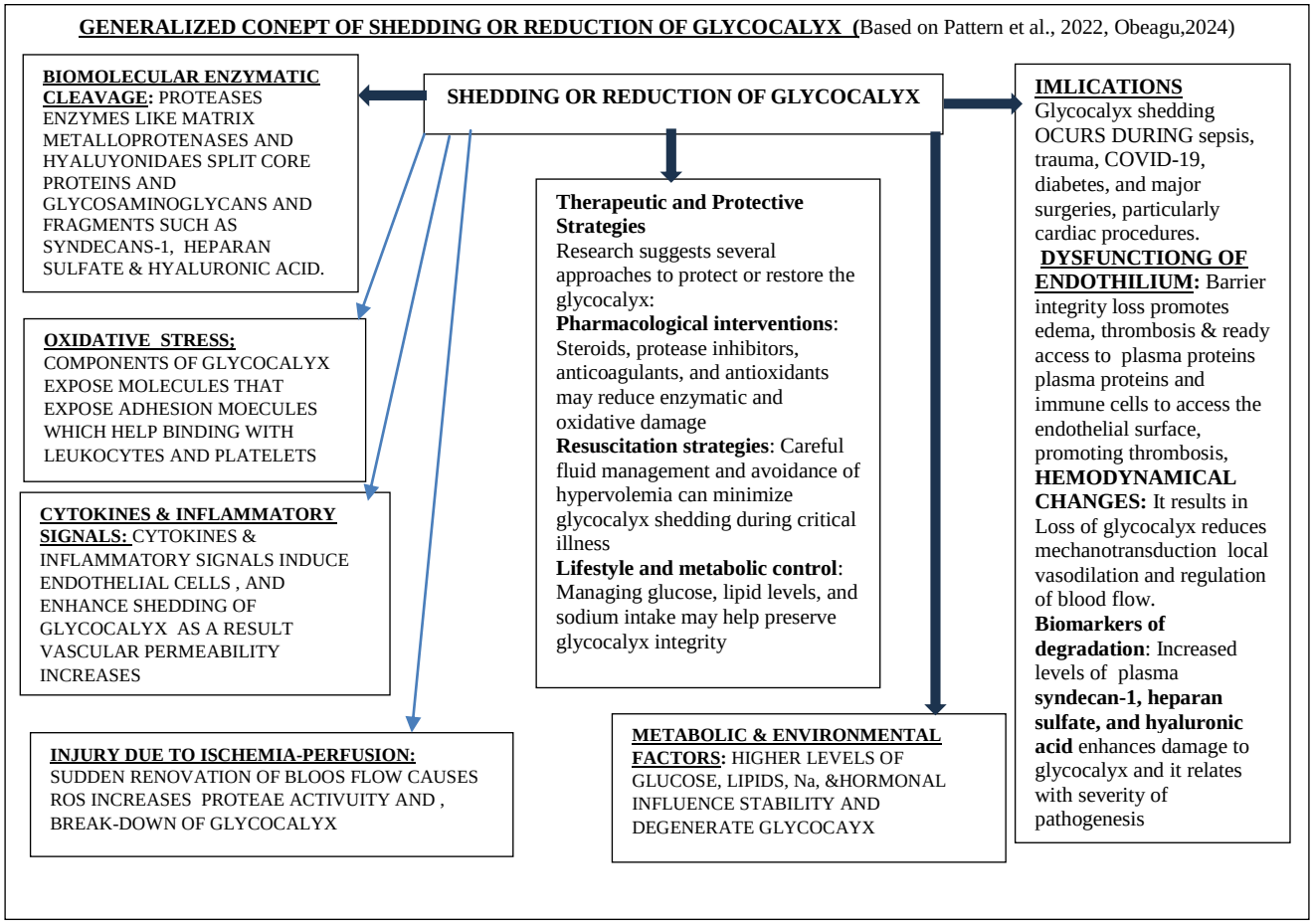
Cartilage-a connective tissue, is rich in multi-territorial extra cellular matrix. It performs double functions: i-provides the structural bases to the chondrocytes and ii-maintains the supply metabolites and controls the physicometabolic needs of these cells and issues, as a unit. The ambient medium of chondrocytes is called pericellular matrix (PCM). This pericellular matrix consists of large amount of hyaluronan, proteoglycan aggrecan and non-fibrillar collagen type VI. The chondrocytes and the pericellular matrix together constitute cartilage and are responsible for its structural, functional and metabolic entities of cartilage tissue. The chondron (unit consisting of chondrocyte or small group of cells surrounded by pericellular matrix) is the structural, functional and metabolic entities of hyaline cartilage. The matrix rich in fibrillar collagen type II surrounds each chondron. This collagen type-II rich matrix layer in a noncellular autonomous matrix (represents glycocalyx).[52,53,54] The pericellular matrix of articular cartilage is rich in type VI collagen and perlecan.

In the articular cartilage hyaluronan, pericellular hyaluronan and aggrecan play structural and functional roles, The aggrecan tethers the components and acts as a load bearing unit. The aggrecan links with the cell surface and bind the hyaluronan; this linkage is due to either hyaluronan synthase or because of multivalent binding to CD44 [CD44 antigen and it is referred to as cell-surface glycogen and participates in cell-cell interaction, cell migration and cell adhesion. It is also called homing cell adhesion molecules HCAM, phagocytic glycoprotein-1 Pgp-1, Hermes antigen, lymphocyte homing receptor.[55]

The articular cartilage is a mystery regarding its repairs, regeneration, degeneration, impact of senesce and intercell signalling. The hyaluronan synthase-2 synthesises hyaluronan in cartilage /articulating cartilage. The aggrecan helps to organize cell-to-cell spacing in cartilage. Hyaluronan facilitates the process of aggrecan-anchorage with the chondrocytes and endocytosis. During pathogenesis or metabolic disorder, the metabolism of hyaluronan changes in pericellular matrix and also in inter-territorial matrix (glycocalyx of chondrocytes).[54]

Shedding or reduction of glycocalyx

The functional and protective outermost cellular and molecular layer is either becomes thinner, reduced or shed under various biochemical conditions or pathological conditions like inflammation, oxidative stress or due to the effects of enzymatic impact. Generally, the common constituents include glycolipids, glycoproteins (syndecans, glypicans, and CD44), glycosaminoglycans (heparan sulphate, chondroitin sulphate, hyaluronic acid.(refer following chart)



Shedding of glycocalyx is of universal cellular process, more so, during chronic and acute inflammation. It is not in relation to any specifical pathogenesis. It can take place during oxidative stress, metabolic disturbances, more specifically, during ischemia etc. During surgical processes like cardiac and transplantation the degradation is at peak as a result the thickness of glycocalyx declined. During this process the degraded products of glycocalyx are present in higher levels and there is increased rate of permeability during its shedding. But higher amounts of its degraded products are not always related with thinning of glycocalyx. The process of physiology of endothelium undergoes helps in obstructing blood flow, elevated degree of permeability for macro-biomolecules; this increases hypovolemia (a medical state in which there is marked decline in the volume of circulating blood in the body).[56] The degree damage or shedding of is proportional to the levels of the constituents of glycocalyx in the blood, urine and easily corelated with the pathogenesis and impacts of pharmaceutical used for the treatment.

SHEDDING OF GLYCOCALYX [IN A NUT SHELL]

TIGHT JUNCTIONS AND ADHERENCE JUNCTIONS BECOME FUNCTIONLESS OR DISAPPEAR; GAPS DEVELOP BETWEEN ENDOTHELIAL CELLS; RATE OF PERMEABILITY ENHANCES; EXTRAVASATION (LEAKAGE) OF PROTEINS, FLUID, (TISSUE EDEMA) AND INFLAMMATORY CELLS TAKES PLACE; FORMATION AND LEVELS OF INFLAMMATORY CYTOKINES AND CHEMCOKINES ELEVATES. ESCAPE OF LEUKOCYTES AND ERYTHROCYTES. DEVELOPEMNT OF ENDOTHELIIOPATHY OF TRAUMA TAKES PLACE. THE ENDOTHELIOPATHY REPRSENTS COMPROMISED ENDITHELAL BARRIER, NON-FUNCTIONING OF COSGULSTION AND INFLAMMATION AND FINALLY MULTIPLT ORGAN DYSFUNCTION.

REGENERATION OR FORMATION OR RESUSCITATION AND PROTECTION OF GLYCOCALYX

RESUSCITATION OR REGENERATION OF GLYCOCALYX [IN A NUT SHELL [57-Barry and Pati, 2022]

PLASMA PROTEINS ARE RESTORED; GLYCOCALYX IS PRESERVED; RETENTION OR PRESERVATION OF VASCULR BARIER; RATE OF SHEDDING OF GLYCOCALYX DECLINES; RESTORATION AND INCREASE OF TIGHT AND ADHERENCE JUNCTIONS; ELEVATION NUMBER AND PRESERVATION OF PERICYTES; DECLINE IN LEACKAGE OF LEKOCYTES AND ERYTHROCYTES; DECLINE OF PERMEABILITY; DECREASE OF INFLAMMATORY CYTOKINES AND CHEMOKINES.

In spite of many efforts to solve the mystery of repair the damaged glycocalyx, its biochemical and cytological mechanism of resuscitation of glycocalyx still exhibit lacunae within the mechanism. The investigation concerning sepsis, the restoration of glycocalyx is considered to be standard one. Application of 10% plasma to the affected glycocalyx prevented the leaky endothelial monolayer and withheld the permeability, declined adhesion of leukocyte and restored tight and adherence junctions of endothelium. This observation indicates the desired results and repaired state of glycocalyx.[58] Further, the impact of plasma on the defective and reduced glycocalyx of endothelium as the result of shock due to haemorrhage which reduced the thickness of glycocalyx.[58,59] The administered plasma helped to restore the originality of glycocalyx of endothelium, but this was not possible using lactated Ringer's solution.[60] Another mode to safe-guard the glycocalyx is inhibition of the action of heparnase-1 on it. Prevention of damage to glycocalyx due to endogenous enzymes is to put a check on them and also on the action of shedders of glycocalyx.[61,62] Whenever there is a structural and functional modification in glycocalyx there is a biomolecular need of growth and binding factors; one of the sources of secretion of such molecules is pituitary follicular cells and these cells produce specific growth factor for vascular cellular endothelium.[63]

The beneficial aspects of resuscitation of glycocalyx include proper normal functions and maintain it even during pathogenic conditions like sepsis, shock due to haemorrhage, endotheliopathy of trauma and prevent the vases of dysfunctional coagulation, inflammation. The regulatory efforts of glycosylation play very effective role in this direction and maintain the normal functionalities of the organs.[64] The appropriate density helps to facilitate the derogative impacts of endothelial glycocalyx. The ability of glycan present in glycocalyx to normalise stress related fluctuations and prevent the stress from reaching the adversely affecting cells present in the vicinity.

Role of glycosylation in relation to glycocalyx

Glycosylation is one of the post-translational covalent processes and it is responsible for either adding or removing some functional groups affecting the functionality of protein. Most commonly there is a transfer of polysaccharide group to a specific amino acid residue present in the protein molecule with the help of glycosyltransferase enzymes. This process is understood to be important for the unfolding of functionalities of proteins such as key regulation of function of a protein, adhesion of cells and escaping immune impacts. Abnormal glycosylation is known to be associated with various pathogenic conditions. Still there exist many structural, compositional lacunae in the working of this significant process. The clinical significance of this process relating the sensitivity and working of biomarkers, smaller molecules in relation to drugs, vaccines, other beneficial drugs and therapeutic implications of this process.[65]

It is very logical to understand the mechanism of glycosylation as it involves polysaccharides and proteins. Proteins are the integral component of cell and proteins are a dynamic molecules and exhibit phosphorylation, methylation, acetylation and glycosylation too. The glycosylation concerns with the covalent binding of oligosaccharides as glycosides to a specific amino acid present in protein molecules. The glycans, and amino acids are grouped depending on their type of linkages, namely these are O-glycosylation, N-glycosylation, C-glycosylation and glycosylphosphatidylinositol/ glycophosphatidylinositol (GPI) linkage. Among all the four members the N-glycosylation and O-glycosylation are main type which participate in the mechanisms of pathogenic state and their progression.[66] The molecular structure of glycocalyx consists of glycosylated transmembrane proteins and lipids. These are suitably placed on the outer or external interface of the eukaryotic cells or luminar surface of the epithelial cells forming the inner lining of tubular structures. This dense layer plays significant role during cell-to-cell interactions, pathogens, or invaders and insure immune response respectively. It is quite obvious that the constituent glycosylated complex biomolecules are the products of glycosylation interactions between polysaccharides and corresponding amino acids of proteins and the lipids. The process of glycosylation is very essential for the formation and existence of the cellular glycocalyx.[67] Glycosylphosphatidylinositol (GPI).[67]

Cytohistological And Cytophysiological Aspects Of Glycocalyx Of Vascular Cells

The vascular cells leucocytes and cells of immune systems involve in immune responses and glycocalyx is the first one to participate. These cells are granulocytes (neutrophils, basophils and eosinophils), granulocytes (lymphocytes and monocytes), immune cells-T-cells, B-cells, dendritic cells, macrophages and natural killer cell (NK cells). These cells are present in blood circulation or come in action during any inflammation. These cells have well-formed glycocalyx.[25] Basically, glycocalyx is a cellular product produced in the endoplasmic reticulum and Golgi apparatus (secretive pathways).[25] Newly formed protein chains insert co-translationally within endoplasmic reticulum. [the process of protein synthesis takes place simultaneously with the synthesis of protein involving ribosome). As proteins are synthesized subsequently from the N-terminus to the C-terminus and ribosome guides their folding and interacting with other subunits or move to specific cellular site.[68] It is protective cover made of glycosylated biomolecules, glycoproteins, glycolipids, and proteoglycans. This outer most fluffy or gel or fine grass like layer facilitates recognition of 'self-cell' and 'foreign cells/non-self 'cell'. Further, glycocalyx participate in cell-to-cell communication signalling (molecular and physical), intercell adhesion, and help the immune cells to identify

non-self-cells and self-cells, migration through tissues, recognition of the antigens etc.

All most all 'eukaryotic-cells' in biosystem have glycocalyx, more so among mammals. Blood cells like erythrocytes (non-immune cell).[9,69] leucocytes, other immune cell like T-cells, B-cells, dendritic cells, macrophages and natural killer cells (NK-cells) have well defined glycocalyx.[25] Leucocytes, such as, granulocytes (neutrophils, basophils and eosinophils) and agranulocytes (lymphocytes and monocytes) have specific sized glycocalyx, and help them to carry out their interactions with structure of another cell. These interactions involve adhesion to endothelial cells when these extravasate (leakage of fluid components) and migrate to the site of their interactions within the biosystem. T-lymphocytes have glycocalyx with more of glycoproteins like CD4/CD4+ (with cluster of differentiation 4, cluster of differentiation.[8] CD8/CD8+ CD4 cells and CD8 cells have 4 and 8 cluster of differentiation are named after proteins on their surface) and T-cell receptors. These glycoproteins present in the glycocalyx facilitate in identification of antigen, during activation process these proteins communicate involving signaling mechanism and from immune synapse between these cells and the antigen. Beta cells (B-lymphocytes) have B-cell receptors, which are present in their glycocalyx along with other surface glycoproteins. This glycocalyx facilitates the binding with antigen, clustering receptors, and interactions with T-cell helper. The glycocalyx of dendritic cells participates in capturing antigens, formation of immunological synapsis with T-cells. The glycocalyx of macrophages participates in the process of phagocytosis, identification of pathogen and ensure cellular communication amongst other immune cells. This glycocalyx modulates the response of inflammation. The glycocalyx of natural killer cells i.e., N K Cells, corroborates recognition of target cells, adhesion process, release of cytotoxic granules when elimination of virus-infected and tumor cells. Thus, glycocalyx of immune cells is very dynamic component and functional in nature. It ensures the adhesion of cells and cellular migration through arteries, veins, capillaries and the tissues. It forms synapsis with immune cells during identification of antigen; it protects cells form the impact of shear stress during their presence in circulation.

During immune activation, there arises the need of adjustment or modulation of signaling receptors, the glycocalyx of the immune cells help such modulations.

Thus, the glycocalyx of immune cells promotes and protects structure and functionality of the immune cells by monitoring signalling process, intercellular interaction, activities of effectors and overall functionality of immune cells.[22,70]

In addition to the above responsibilities, the glycocalyx also actively regulates the cellular movements in the blood vessels. The glycocalyx has the ability to modify its size as per the need; it can prune its size (thickness) depending on the immune response with respect to the inflammation state and the needs of cell migration and effectiveness of immune response. Glycocalyx play a significant and regulatory role during the movement of immune cell via blood flow more specifically in the inflamed tissues; this is observed during skin defects like psoriasis. The glycocalyx present on the cells of blood-vessels facilitates the recruitment of immune cells under normal and affected conditions.

This possibly due to the specific interactions between itself and immune cells more so during navigation of blood in the affected and normal tissues. During pathological conditions or the onset of pathogenesis the process of shedding of glycocalyx performs double functions i.e., it facilitates the movements of immune cells and helps in fighting infection and selective regulation of movements of immune cells towards the site of infection.[22,70,71] Glycocalyx actively participates in almost all cellular activities and its behaviour. Its role is very important during normal healthy state and also during diseased state including the inter cellular interactions/behaviour. This cellular component helps in identifying healthy cells and differentiate between transplanted cells, diseased cells, and invading organisms or pathogens. It plays significant role during cell-cell adhesion and cellular migration during embryonic development. Understandably, it also plays an essential role during functionality of immune cells and therapeutic interactions or manoeuvring.[72]

Glycocalyx shows two distinct regions, the interface of the region tightly attached to the plasma membrane is the (inherent part) and an outer region which may be attached to extracellular matrix or may be free (in case of freely moving in body fluids). Biochemically, glycocalyx consists of glycolipids, glycoproteins, oligosachharide and glycoproteins as trans membrane proteins. Transmembrane glycoproteins like selectin-E, selectin-P and selectin-L facilitate the recognition of specific oligosaccharide present on the membrane of the interacting cell or organism. This feature is very useful during adhesive interactions among endothelial cells. Such oligosaccharides behave like "cell markers" and help to distinguish between different type of cells. The trans-membrane glycoproteins present on the membranes of endothelial cells and leukocytes interlink with help of fucose, galactose, N-acetylglucosamine and N-acetylneuraminic acid (also called sialic acid). The N-acetylneuraminic acid is commonly present at the terminal end of the cell surface glycan in most of the mammalian cells and it plays functional role in "'cell to cell recognition" and modulations during immune responses.[2,72,73]

Reitsma et al. reported that the endothelial glycocalyx is carbohydrate enriched layer on the endothelial cells in the blood vessels; broadly, it may be considered to be a

meshwork consisting of soluble molecules.[5] These molecules are derived from plasma and/or endothelium. Under normal conditions there exists a dynamic balance between the flowing blood and the soluble components of glycocalyx; this equilibrium affects the thickness and the composition of glycocalyx.[5] Based on the nonquantitative studies on glycocalyx it is made of proteoglycans, glycosaminoglycan, and glycoproteins. Proteoglycans include syndecans and glypicans, other being mimecan, perlecan, and biglycan, these may diffuse in blood stream but reside in glycocalyx.[73,74] There are five glycosaminoglycans, namely, heparan sulfate, chondroitin sulfate, dermatan sulfate, keratan sulfate, and hyaluronan; these have varied functions.[75,76]

Although glycocalyx covers the boundary of a cell either from all sides or at least their free sides. This biochemical fluffy coat protects, help in intercellular communication (both physical and biochemicals) and also influence the inter-cellular interactions.

Role of glycocalyx during thrombomodulation

Glycocalyx plays significant interactive role during thrombomodulation. The glycocalyx regulates the interactions between various solutes and the endothelium of the blood vessels. This velvety biochemical luminal layer controls the intensity of cellular interactions due to its ability to either mechanical interference or obstructive nature. Earlier, it was considered to act as one of the limiting factors which controls the interaction between erythrocytes and the endothelial cells. Further, the changes in the thickness of glycocalyx heparinase enzyme dissociate heparan-sulfate chains and change the 'hematocrit value' of blood flowing in capillaries. It was also suggested that physiological stimuli have an ability to change the thickness of glycocalyx.[77] In this process, even platelets and white blood cells are also included.[36] Currently, it is considered that platelets do not make contact with epithelial cells of blood vessels and prevent unwanted clot formation. The thickness of glycocalyx varies in main blood vessels and reduces as their diameter reduces towards capillaries (from 3 µm to 0.5 µm). The glycocalyx and epithelium of the blood vessels offers steric impediment with respect to platelets. The molecules of adhesion present on the cellular surface have practically no access to the molecular interacting entities but this is made possible because of some perturbation occurring on the surface of glycocalyx. Thus, the interaction between platelets and endothelium in normal state do not take place but if the surface is favorable for thrombosis then the interactions take place.[78] Some of the molecular features of the glycocalyx control the formation of clot. This functional feature is in addition to the steric capability of the molecules of glycocalyx. Molecules like glypican binds with antithrombin-III because of its high affinity. The antithrombin-III is located on the surface of cells of endothelium and this property helps in the antithrombotic ability avoiding clot formation. Heparan sulfate can pin-point antithrombin-III and react with it.[36,79] The interaction of glypican with antithrombin-III seems to be a mystery because it shows high degree of reactivity in comparison to other proteoglycans although they are similar proteoglycans.[80]

It seems that molecular affinities between the different glycosaminoglycans (GAGs) having similar basic core conformation which is likely to facilitate the said molecular interaction. But their higher and different level of overall conformational arrangement may be responsible for their different levels of reactive affinities.

The glycocalyx possesses adhesion molecules, these molecules help during their binding with platelets and also in the clotting process. Molecules like P-selectin is collected in endothelial cells as 'Weibel Palade bodies'.

These move to the cell surface when the endothelium gets activated due to the presence of the inflammatory factors such as histamine and thrombin.

Thus, the P-selectin and PECAM [Platelet endothelial cell adhesion molecule; CD.[31] help the process of adhesion and start the formation of clot.[81,82,83,84,85] The P-selectin granules are also present in platelets, on activation of platelets, these are released for action. When chronic inflammation occurs, the platelets and some cells of endothelial cells express P-selectin glycoprotein ligand-1. It helps the binding of platelets during the formation of clot.[86,87] Platelets liberate a specific enzyme called 'platelet endoglycosidase', it hydrolyses endothelial heparan-sulfate, mostly under condition favorable to clotting process. This enzyme further interacts with the core of proteoglycan and leave very less or no heparan sulfate chain attached to the cell.[36,88,89,90] Mostly, 'endothelial ligands' for the P-selectin molecules present on the platelets are short and are not exposed due to glycocalyx. When the glycocalyx gets degraded, these molecules become exposed to react with adhesion molecules. It has been seen that at least one luminal integrin 'aVb3' participates in the formation of clot. The endothelial integrin 'aVb3' forms a bridge like link with fibrinogen, fibronectin and von Willebrand factor and it helps the linking the platelet with cells of endothelium.[91] Thus, it is obvious that the role of glycocalyx is significant in the formation of clot.[36]

Role of glycocalyx during immunological and inflammatory responses

From molecular point of view, the process of downgrading and upgrading of glycocalyx suitably respond during immunological interactions as well as infection conditions. Inflammation directly affects the glycocalyx. This complex, polysaccharide protein fluffy layer is present on the luminal side of vascular endothelial cells, cells freely floating in the blood and other body fluids like lymph, cerebrospinal and interstitial fluids. The reduction on glycocalyx is likely to enhance inflammatory response and may result in diabetic and atherosclerotic conditions. Since, one of the

prime functions of glycocalyx is the maintenance of homeostasis among vascular tissues/cells. The reduction in glycocalyx due to inflammation results in dysfunctioning of endothelia. This reduction in glycocalyx also acts as a cause of onset of conditions like coagulation and defective immune response. It is quite understandable that the interaction and the mechanism involved between inflammation and glycocalyx is helpful in the development of remedial therapeutic agents for the ailments of vascular pathogenesis and also for the treatment of inflammatory conditions.[92,93,94]

Glycocalyx performs very essential functions like, barrier for the endothelial permeability, stability, transduction of forces (physical) develops between vascular lumen and walls of vessels, it provides binding sites to many growth factors and vasoactive agents; it also helps the binding of platelets, migrating leukocytes whenever inflammatory response has to be performed. Good numbers of processes involve a specific amount of intracellular Ca^{++} and it exhibit fluctuations depending on the cellular physiological status. Intracellular level of calcium depends on the amount of the endothelial cellular Ca^{++} and a specific mechanism. The endoplasmic reticulum provides this Ca^{++} but the mechanism involved is not well understood.[94]

Inflammation is a 'fighting and recovery response' to the invasion of pathogens, cellular-insult (physical and chemical or biomolecular), allergens, physical injury. If it persists for long duration or it becomes chronic, leads to disease. It can be internal as well as external. It is readily identified due to the presence of redness, swelling, painful (sometimes), heat, dysfunctioning/misfunctioning of the tissue/organ. During the persistent inflammation, the mode of giving response gets dysregulated which may be due to another reason and leading to pathogenesis. Mostly, cellular necrosis is the initial stage of inflammation but apoptosis restricts inflammation. The senescence process takes place in variety of living cells, dying and the death state influence the inflammatory phase differentially. It has been observed that mechanism of injury and pathogenic state has some similarities with the mechanism of inflammation.[95]

Whenever there is an injury, cells, like neutrophils, macrophages of innate immune system start functioning in an orchestrated manner. These efforts help to maintain homeostasis and neutrophils recruit platelet and degranulate the cytokines and growth factors. Mast cells release antimicrobial peptides, molecules which breakdown the extracellular matrix and enhance the permeability of ambient blood capillaries or blood vessels. Neutrophil facilitate decontamination of wound using phagocytosis of pathogen and the presence of pro-inflammatory signalling molecules produced the facilitate decontamination process. These steps elevate the degree of activation and recruitment of more of immune cells. The monocytes and the macrophage present in the tissue help in production of cytokines; these create specific environment for inflammation which is rich in debris and phagocytosis clear these debris. Other participating components are signaling molecules, antigen, products of these cells and dendritic cells also join in 'adaptive response' against the pathogens.[96] The neutrophils undergo apoptosis and their debris are eliminated within one day after their arrival.[97] These cellular debris must be removed from the site and 'efferocytosis (apoptotic destruction of neutrophils) or phagocytosis' carryon this clearance. This mode to clears the debris is about 10^9 apoptotic cells in a day from the site of injury without involving immune response. When macrophages eliminate neutrophils involving efferocytosis post injury, the macrophages directly transit from inflammation state to repair and regeneration mode. This change is phenotypic in nature and plays significant role in resolving inflammatory state and restores the functions of the specific tissue.[98,99,100]

It is established that infiltration of macrophages and activation due to proinflammatory agents are important for the process of tissue repair and also for maintaining specific homeostasis.[101] Further, macrophages should be polarized in order to interact with anti-inflammatory agents and there is a need of pro-regenerative phenotype to ensure complete repair of wound.[102,103,104,105] Cell undergoing or have undergone apoptosis need clearance by macrophages, for this engulfment, the receptors on the macrophage get molecularly linked with surface markers of apoptotic cells and helping their recognition, uptake and signalling between the interacting entities. During this interaction the exposure of the phospholipid phosphatidylserine facilitates the specific apoptotic signalling between these cells. *In vitro* experiments, the live cells the phospholipid phosphatidylserine is restricted within the cell, the 'flippase enzyme' which is lipid transporter protein, this component transport lipids from the peripheral leaflet (outer part of cell-membrane) to the inner leaflet (inner part of cell-membrane); as this process proceeds, these layers develop anisotropic forms. On the onset of cellular apoptosis, the cellular membrane attains anisotropic form and exposes the phospholipid phosphatidylserine (which is located on the outer leaflet).

This status relates to 'eat-me' invitation as pro-phagocytosis for engulfment by the macrophages and which undergo polarization as pro-resolving phenotype.

This phenomenon plays significant role in reduction of inflammation. As a result, damage of the tissue gets restricted and initiation of regeneration of the affected tissue.[106,107,108,109] Initially, this physiologically process is a defensive, healing process and facilitates elimination of injurious stimuli/cues. This phenomenon helps to maintain the homeostasis of the tissue and resolve the acute inflammation. If the acute inflammation becomes chronic, mostly, that leads to serious inflammatory pathogenesis.[110] Intermittent elevation in inflammation may promote the survival intentions. When there is a

physical injury or infection, there are greater chances of promotion of chronic inflammation under specific socioenvironmental conditions and lifestyle of the individual. This state induces 'systemic chronic inflammation' which is likely to result in disability/diseases like cardiovascular condition, cancer, diabetes mellitus, chronic renal disorder, non-alcoholic fatty liver, autoimmune and neurodegenerative disorders.[111] Parameters like pathogens, damaged cells, abuse and toxins are also capable to inducing inflammation (acute and chronic) and affect heart, pancreas, liver, kidney, lungs, brain, gastrointestinal tract and reproductive system. Further, these also trigger inflammatory signalling pathways like NF-κB, MAPK (Mitogen-activated protein kinase pathway), JAK-STAT pathways (Janus kinase- group of intracellular, non-receptor tyrosine kinases) these transduce cytokines mediated signals. It has two 'near identical phosphate-transferring domains; one domain shows kinase activity and the other negatively controls the kinase function of the first function.[112] A specific extracellular cue initiates the activation of a MAPK (it has six cascades), the interaction between small GTPase and/or phosphorylation due to protein kinases involving molecular signaling cascades, also, called transduction pathways, that converts or change extracellular cues/messages, may it be hormones or growth factors into cellular responses like, survival efforts, cell division process or any response of cell. Whenever, the Mitogen-activated protein kinases interacts with many substrates present in cytosol and nucleus resulting in fluctuations in protein functionalities and expression of gene. These changes focus on the cell response towards the mechanical cue or messenger or stimulus.[113]

During infection leukocytes gets responsive and interact with endothelium under the regulation of glycocalyx. The glycocalyx offers steric resistance during interaction between leukocytes and cells of epithelium; this interference is more less is similar to that of interaction between endothelium and platelets. There is a distinct degradation of glycocalyx when exposed to adhesion microspheres coated with ICAM-1 antibody. There is a clear degradation of glycocalyx due to exposure of adhesion molecules and ligands as these molecules represent the state of inflammation.[36,114] The oxidized low-density lipoproteins elevate the rate of localized aggregation of leukocytes as a result of administration of heparan and heparan sulfate.[115] Heparan and heparan sulfate have been found to reduce the intensity of reduction of thickness of glycocalyx. Further, this type of reduction in the thickness of glycocalyx is also observed in the individuals suffering from sepsis and ischemia/reperfusion; this observation indicates the importance of the reduction of glycocalyx for the successful adhesion among leukocytes and infiltration.[116,177] When heparan and heparan sulfate bind with P-selectin, L-selectin and 6-O-sulfation, the resultant products of these interactions have ability to exhibit anti-inflammatory behavior.[118,119] These observations using exogenous heparan and heparan sulfate are observed in the affected subjects. The endogenous proteoglycan-bound heparan and heparan sulfate also interact with P-selectin and L-selectin also have the ability to inhibit inflammation. These examples ensure that heparan sulfate is one of the ingredients in the interaction between leukocytes and localized inflammation. The impacts of cleaved entities can cause the reduction of glycocalyx during inflammatory process. NF-kB is an enhancer to activate B-cells; the dermatan sulfate present in circulation activate NF-κB in the cells of endothelium. (Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) is a family of transcription factor protein complexes that regulate transcription of DNA, cytokine production and cell survival.[120] This molecule also controls the expression of adhesion molecule such as ICAM-1 (Intercellular Adhesion Molecule 1) and VCAM-1 (Vascular Cell Adhesion Molecule-1) and many important cytokines and chemokines, which relates with inflammation.[36,121] The fragments of soluble heparan sulfate behaves like a ligand for 'Toll-like receptor-4, it triggers the formation of cytokines related to proinflammation.[122]

The constituents of degradation of glycocalyx induce 'Toll-like' receptors. The path way of NF-κB is the bases of mechanism involved in inflammation and it can be regulated via degradation of glycocalyx components. Good number of constitutes of glycocalyx participate in the movements of white blood cells, adhesion, and squeezing of leukocytes through walls of blood vessels to reach the target of the physiological functions (diapedesis). Hyaluronic acid helps the process of extravasation of white blood cells at initial stages and this action is of significance during localized inflammatory responses. TN-Fa (Tumor necrosis factor alpha plays a primary role during inflammation, immune system development, apoptosis, and lipid metabolism. TNF-alpha was first identified as a 'cytotoxic factor'. Macrophage produce it and it is capable of killing mouse tumor cells.) signalling regulates the localization of hyaluronic acid on the surface of endothelial cells; this action is successfully accomplished when hyaluronic acid binds with CD44.[123] Lymphoid cells readily get linked and move on the CD44 and linked with hyaluronic acid.[124]

Biomolecules like E-selectin and P-selectin help the involvement of leukocytes and their linking to activated platelets and also activated endothelial cells.[125,126] In addition to these processes, the endothelial vascular cell adhesion molecule-1 (VCAM-1) and Intercellular Adhesion Molecule-1 (ICAM-1) bring about the tight linking with leukocytes and the process is called 'adhesion'; these steps bring he cells close to each other and to endothelial cells.[127,128]

Thus, at last, Platelet Endothelial Cell Adhesion Molecule (PECAM) a transmembrane glycoprotein) control the movements of leukocytes through endothelial

cells. These cells use the path between adjacent endothelial cells and movement of leukocytes through basement membrane.[36,129] Under normal physiological state, the molecules like E-selectin, P-selectin are not present on the surface of cells of endothelium; when the cells of endothelium get activated with the help of TNFa these molecules are found on these activated cells. The intensity of activation is further enhanced with the help of adhesion molecules such as intercellular adhesion molecules-1 (ICAM-1) and Platelet Endothelial Cell Adhesion Molecule (PECAM).[126,130] Whenever and wherever the inflammation exists, the endothelial cells also get activated, thus, these conditions favour aggregation of leukocytes. During this process, NF-kB, this molecule upgrades with the help of molecules from the degraded glycocalyx. NF-kB molecule is a participant of TNFa-pathway and it modifies endothelium on the onset of inflammation.[121,131] The capacity of endothelium to degrade facilitates the exposure of binding sites present on the adhesion molecules while the ability to upregulate helps in manifestation of the adhesion molecules; thus, over all, the endothelium provides the suitable proinflammatory and anti-inflammatory mechanisms.

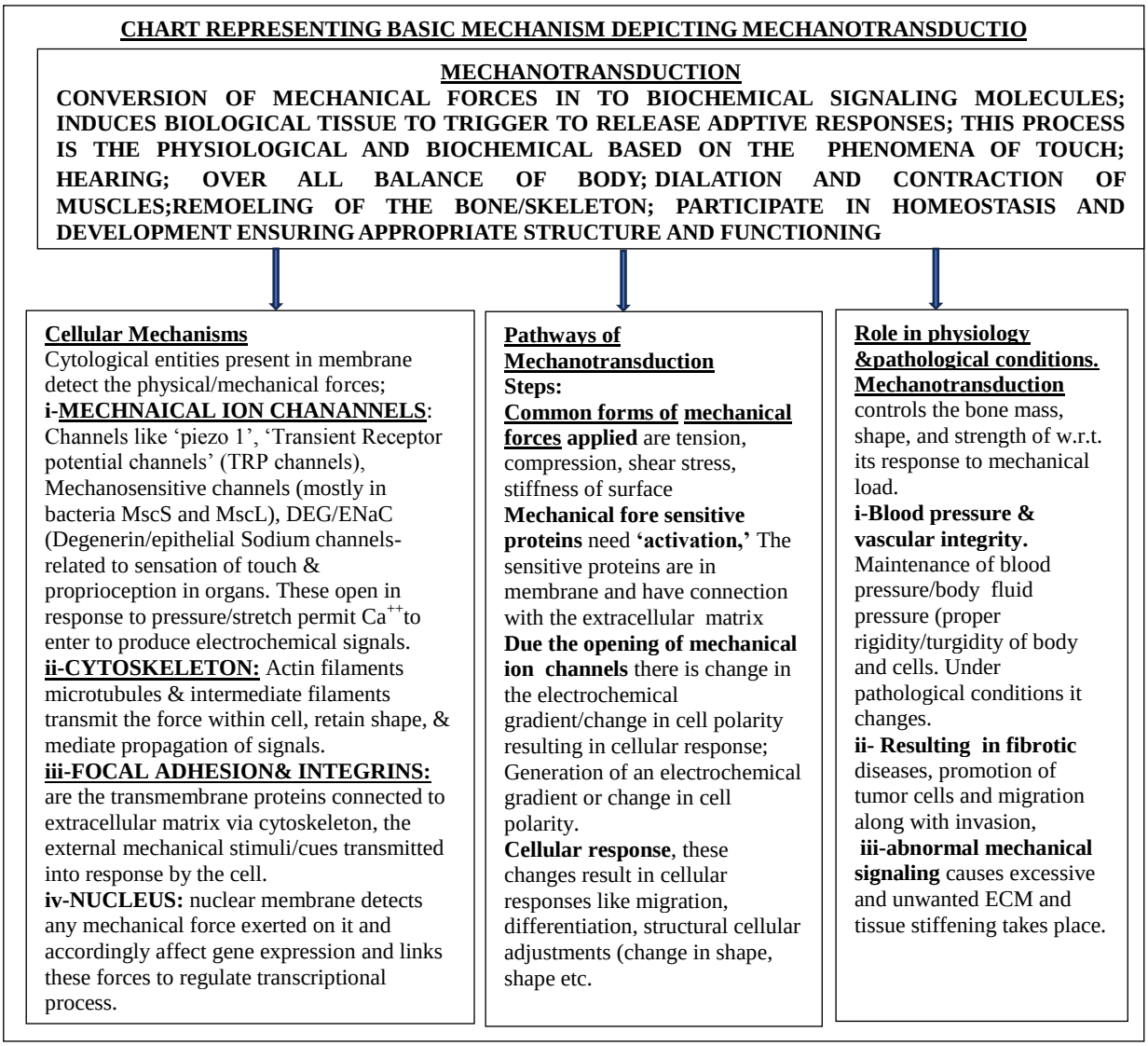
There exists anti-inflammatory mechanism. The GAG-antithrombin-III molecular interaction works to restrict inflammation with help of non-antithrombin pathway. There are many lacunae in understanding of this pathway. It involves is the result of reduction of the contact/link between the cells of endothelium and the leukocytes.[132,133] The role of E-selectin appears to be a complex phenomenon. Its role in the process of angiogenesis is very enlightening.

Currently, angiogenesis is considered to be non-inflammatory phenomenon as it involves the main role of leukocytes and very less participation of constituents of endothelium. Heparan-sulfate masks the molecule E-selectin and its interaction with leukocytes; this interaction plays important role during angiogenesis, more specifically, during their interactions with white blood cells. It also helps to utilize the cells of endothelium at the site of angiogenesis. Further, the binding of E-selectin with endothelial cells may be under the control of molecules like heparan/chondroitin sulfate proteoglycans such as syndecan-1.[36,132,134]

Basic concept of mechanical signal transduction and role of glycocalyx

During embryonic development specific location is assigned to a particular site for an organ called formative zones in the embryo. These locations are the most convenient for the structural and functional aspects of that specific organ. The embryonic cells would be involved to reach or to carry themselves to the respective sites because of formative movements. The glycocalyx is located in such position that it performs the assigned functions like identification and interactions with any type of invader or any agent that abuses the biosystem. Hence, its location is well suited to sense the mechanical cues and convert them in to biochemical signals which are conveyed to the concerned cell to release the appropriate response. The conversion of mechanical cue/stimulus in to biomolecular signal is transduction. The mechanical stimulus is the sheer stress and sensing it. This sensation (mechanical message) gets converted into chemical signals. These signals are conveyed to the appropriate center with the help of signalling pathways. The glycocalyx is present at the luminar location and can readily sense the sheer stress conveniently, hence, it plays significant role in its detection process and release the response. There appear to be three zones of the thickness of glycocalyx; inner most, innermost and touching cell membrane, the middle zone and the outer most zone. The outermost zone is the first one to be in contact with extra cellular medium and is receptive to any types of fluctuation physical, biochemical, contact with toxic substance, allergen or pathogen. The thickness varies in the blood vessels and more so the site of bifurcation (branching sites). The inner most zone and middle zones experience or affected lesser degree of strain-stress but associate more securely with cell membrane as compared to the outermost zone.[2,135]

The luminal margin of endothelial cells has varied types of membrane bound macromolecules that constitute glycocalyx. This specific molecular layer is effective in sensing the force (sheer stress) caused due to blood flow and able to transform this physical force through cytoskeleton. This physicochemical message moves to the site of transduction into biochemical response. The specific structural and functional aspects of glycocalyx play significant role in the process of mechanotransduction and structural and functional re-orientation that maintain its normal and activated statuses. The structural and functional investigations involving enzymatic interactions. Specifically, ‘glycosaminoglycan’ constituents indicate its role as mediator in the process of ‘mechanotransduction’.



The force (sheer-stress) develops due to the formation of 'nitric oxide' one of the parameters related to 'cardiovascular control' but when prostacyclin is formed in the endothelial cells, there is no such impact related to on sheer-stress. Further, this observation reflects on the selected distribution of sites of mechanotransduction along the endothelium cells. The cytoskeleton and intercellular junctions play major role during the remodelling of endothelium to perceive and response to sheer-stress and this functionality involves predominantly glycocalyx.[136] The glypican helps in transducing mechanical signals/cues, along with plasma membrane associated biomolecules, control the formation of nitric oxide; this also indicates the position of site of this activity within caveolae together with enzyme endothelial nitric oxide synthase.[137] The mechano-sensing ability to detect the fluctuations caused due to the blood flow relates with G-protein coupled receptors, signalling pathways, and conformational variations caused in glycocalyx.[138] In the current times, the investigations reveal the role of glycocalyx helping specific signaling related to mechanosensing ability. The transmembrane proteins such as syndecans, have their terminal COOH- group is linked with the membrane protein (syndecans). This link facilitates and regulates the rearrangement with cytoskeleton and detecting the fluctuations occurring in the ambient extracellular environment.[139] When the detection of fluctuations due to nitric oxide in endothelial cells is noticed, there is a need of the related enzyme for such interaction, the sheer-stress activates gene to express to produce 'endothelial nitric oxide synthase', 'cyclooxygenase-2', 'von Willebrand factor' and 'VE-cadherin' in the cells of endothelium (in this case the cells of endothelium of mouse as test sample).[140] It has been observed that the when shear-stress related gene expression is needed and if heparinase-III is present then the intensity of such expression is highly declined. This process reflects that the proteoglycans having heparan sulphate side chain participate in mechanosensation directly or indirectly. There is a possibility of the involvement of mediation for the response to take place in any possible mode. There exists a specialized link between the components of glycocalyx and mechanotransduction; the shear-stress

inhibits due to break down of heparin sulphate but this is not so when chondroitin sulfate splits and detect shear-stress induced nitric oxide.[141] The role of any type of GAGs related to protection is capable to find out/analysed the features of proteoglycan which is able to study and detect signalling pathways completely dedicated to this type of sense from the extracellular environment. The breakdown of hyaluronic acid because of hyaluronidase has the ability to prevent shear-induced the formation of nitric oxide.[142] The shear-stress can affect the thickness of glycocalyx. In cells of endothelium, when exposed to shear-stress the regulated production of hyaluronic acid gets affected.[143]

CONCLUSION

Ongoing discussion on glycocalyx reflects on its structural and functional significance and degree of adaptability under normal and stressed conditions. The process of glycosylation is of functional significance and it interacts with polysaccharides group of some specific amino acids residue, proteins and lipids. This interaction is enzyme oriented. The fluctuations in the structure of glycocalyx in varied performances like immune response, transduction of physical cues (stimuli-forces), immunological responses, thrombomodulation, and pathogenesis is evident. The process of its changing thickness relates with shedding, resuscitation and endoplasmic permeability. The capacity of endothelium to degrade, facilitates the exposure of binding sites present on the adhesion molecules: while the ability to upregulate helps in manifestation of the adhesion molecules. Thus, over all, the endothelium provides the suitable proinflammatory and anti-inflammatory mechanisms. Although, this cellular component is present at the periphery of all cells and influences most of the cellular functions. It plays very significant role from pharmaceutical aspects so that remedial suggestions can be successfully implemented. The endothelium provides the suitable proinflammatory and anti-inflammatory mechanisms. Angiogenesis is considered to be non-inflammatory phenomenon as it involves the main role of leukocytes and very less participation of constituents of endothelium. There is need of further investigations related to its structural and functionalities because there are mechanisms not well understood. The endoplasmic reticulum provides this Ca^{++} but the mechanism involved is not well understood.

ACKNOWLEDGEMENT: Author extends his gratitude to all authors/researchers whose work has been referred. Conflicts of Interest: Author declares no conflict of the statement.

Funding: No funding is needed for this presentation.

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