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Elastic Fibers and Elastin Receptor Complex: Neuraminidase-1 takes the center stage

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Abbreviations: EBP, Elastin Binding Protein ; ECM, Extracellular Matrix ; EDP, Elastin-Derived Peptides ; ERC, Elastin Receptor Complex ; EMILIN, Elastin Microfibril Interface-Located protein ; LTBPs, Latent-TGF β -Binding Proteins, MAGPs, Microfibrils-Associated GlycoProteins ; MFS, Marfan syndrome, Neu-1, Neuraminidase-1, PPCA, Protective Protein/Cathepsin A, , RER, Rough Endoplasmic Reticulum, SA, Sialic Acid ; TGF- β , Transforming Growth Factor- β .

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Abstract

Extracellular matrix (ECM) has for a long time being considered as a simple architectural support for cells. It is now clear that ECM presents a fundamental influence on cells driving their phenotype and fate. This complex network is highly specialized and the different classes of macromolecules that comprise the ECM determine its biological functions. For instance, collagens are responsible for the tensile strength of tissues, proteoglycans and glycosaminoglycans are essential for hydration and resistance to compression, and glycoproteins such as laminins facilitate cell attachment. The largest structures of the ECM are the elastic fibers found in abundance in tissues suffering high mechanical constraints such as skin, lungs or arteries. These structures present a very complex composition whose core is composed of elastin surrounded by a microfibrils mantle. Elastogenesis is a tightly regulated process involving the sialidase activity of the Neuraminidase-1 (Neu-1) sub-unit of the Elastin Receptor Complex. Interestingly, Neu-1 subunit also serves as a sensor of elastin degradation *via* its ability to transmit elastin-derived peptides signaling. Finally, reports showing that neuraminidase activity is able to regulate TGF- β activation raises questions about a possible role for Neu-1 in elastic fibers remodeling.

In this mini review, we develop the concept of the regulation of the whole life of elastic fibers through an original scope, the key role of Neu-1 sialidase enzymatic activity.

Keywords : Elastin, Elastin-Derived Peptides, Elastin Receptor Complex, Neuraminidase-1, Desialylation

Introduction

Extracellular matrix (ECM) is a network of macromolecules surrounding cells in all tissues. Although it has been considered for years as a simple architectural support, providing structural and mechanical functions, it is now clear that ECM also mediates diverse biological functions and influences cell phenotype. This highly complex and dynamic network is composed of several macromolecules playing distinct and precise roles involved in tissue function, integrity and homeostasis [1]. Among these proteins, collagens appear as main structural contributors of the ECM and are responsible for tensile strength [2]. Proteoglycans and glycosaminoglycans have the ability to sequester water allowing resistance of tissues towards forces such as compression, and several glycoproteins such as laminins or fibronectin act as cell attachment facilitators [3].

Elastin, another fibrous protein, is involved in tissues elasticity and resilience enabling them to withstand repetitive mechanical stress. It is consequently found in highly deformable tissues such as skin, lungs or arteries [4, 5], where this highly elastic protein plays a crucial role in their physiological function. One extraordinary example of elastin fundamental function is the adoption by vertebrates of a close circulatory system using a specialized vessel wall designed to provide essential elastic recoil at high pressure [6, 7]. This wall, highly rich in elastin that accounts for up to 50% of the protein content of the aorta [8], presents an interconnected lamellar network of elastic fibers, responsible for transfer of the deformation stress throughout the wall, a process which is essential for vessels function [9].

Elastin is the main component of a more complex supramolecular assembly named elastic fibers, the largest structures in ECM [10]. Elastic fibers are composed

of a core of elastin, a polymer of tropoelastin, surrounded by a mantle of microfibrils whose composition is complex. These fibers are assembled primarily during development and childhood. Besides their elastic properties, they also present the ability to sequester highly active growth factors such as latent Transforming growth factor- β (TGF- β), regulating its bioavailability and activity [11, 12]. Although elastic fibers are designed to maintain elastic function for a lifetime and consequently are highly resistant to degradation, several enzymes (matrix metalloproteinases, serine proteases or cysteine proteases) are able to cleave elastic fibers [8, 13]. This leads to loss of tissue elasticity contributing to the ageing of ECM but also to the development of pathologies such as emphysema, aneurysms or atherosclerosis in which the elastin-derived peptides (EDP) produced play a central role [14-16].

The Elastin Receptor Complex (ERC) has been shown to be actively involved in some of the above mentioned processes through its participation in elastogenesis but also as a sensor of elastin degradation *via* its ability to bind EDP. In these two phenomena, reports clearly pointed out the central role of the sialidase activity of its Neuraminidase-1 (Neu-1) sub-unit [17, 18]. Neu-1 now clearly appears as the fundamental actor in the homeostasis of elastic fibers, playing a role during their synthesis but also being a crucial sensor of their degradation. Finally, reports showed the importance of sialidase activity in the regulation of TGF β activation, suggesting an unexpected role for this enzyme class [19]. This opens new avenues for a role of the ERC and especially Neu-1 in the biochemistry, biology and functions of mature elastic fibers.

Based on this evidence, we summarized in this mini review the role of Neu-1 in the regulation of the whole life of the elastic fibers. We highlight the original concept of the regulation of elastic fibers from their biosynthesis to their degradation

via an innovative and not previously discussed point of view, the crucial participation of a sialidase, Neu-1.

Elastin Receptor Complex-associated Neuraminidase-1 : a crucial actor of elastic fibers biosynthesis

The formation of elastic fibers requires the coordination of several complex processes. It involves intracellular regulation at the transcriptional and post-transcriptional levels, extracellular secretion and assembly of tropoelastin monomers at the site of elastogenesis. Tropoelastin secretion is followed by its maturation involving cross-linking through lysyl oxidase (forming diverse cross-links such as lysinonorleucine, desmosine or isodesmosine) [20] and its association with the preexisting microfibrils scaffold composed of several classes of glycoproteins such as fibrillins, Microfibrils Associated Glycoproteins (MAGPs), fibulins, Latent TGF- β Binding Proteins (LTBPs) or Elastin Microfibril Interface-Located proteins (EMILINs) [21]. The components of elastic fibers are synthesized and secreted from several cell types including smooth muscle cells, fibroblasts, endothelial cells, chondroblasts and mesothelial cells [22], with tissue-specific expression of elastin during development [23]. Importantly, elastogenesis is a process that generally ceases in childhood with little or no renewal of elastin production during adult life, thus exposing elastic fibers to diverse types of alterations [8].

After its synthesis and splicing, tropoelastin mRNA is exported outside the nucleus. Translation occurs at the surface of the rough endoplasmic reticulum (RER) thereby forming in human, for the largest isoform, an about 60 kDa polypeptide with a 26 amino acid signal sequence that is cleaved as the protein enters the RER lumen

[24, 25]. After release of the signal peptide, the protein is transported to the trans-Golgi apparatus. Tropoelastin is then chaperoned by EBP (Elastin Binding Protein), a splice variant of the lysosomal β -galactosidase that limits premature intracellular self-aggregation and degradation by proteinases [26]. Tropoelastin is then accompanied to the cell surface through its interaction with EBP [27]. When reaching the plasma membrane, the latter assembles with Neu-1 and protective protein/cathepsin A to form a cell surface-targeted molecular complex named Elastin Receptor Complex (ERC). Besides EBP, all three components of the complex have been shown to participate in the regulation and assembly of elastic fibers but Neu-1 is clearly a central actor [28].

Indeed, the sialidase activity of Neu-1 that cleaves the terminal sialic acids (SA) of the carbohydrate chains of microfibrillar proteins during synthesis of elastic fibers, leads to access to the galactosyl residues. In turn, exposed galactosugars interact with the galactolectin domain of EBP, to induce the release of transported tropoelastin molecules, facilitating their subsequent assembly into elastic fibers. After release of the tropoelastin to the growing elastic fibers, EBP is recycled back into intracellular endosomal vesicles and can bind and escort a new synthesized tropoelastin molecule to the cell surface again [27] (Figure 1).

Several elegant studies confirmed the essential role of Neu-1 in the synthesis of elastic fibers. The murine knockout of the Neu-1 gene led to abnormal organization of elastic fibers in the aorta with reduced level of elastin [29]. This is associated with abnormalities characteristic of early-onset of sialidosis in children (growth retardation, severe nephropathy, progressive edema, splenomegaly, kyphosis and urinary excretion of sialylated oligosaccharides) [30]. The treatment of human skin fibroblasts, aortic smooth muscle cells and ear cartilage chondrocytes with sialidase

inhibitors suppressed elastic fiber assembly and induced impaired elastogenesis in developing chicken embryos [28]. Moreover, elastogenesis in cultured dermal fibroblasts from patients with lysosomal β -galactosidase, PPCA and Neu-1 deficiencies (such as congenital sialidosis and galactosialidosis) could be reversed by transformation with Neu-1 cDNA, treatment with bacterial sialidase [28] or substitutions in the Neu-1 gene [31]. Those findings clearly showed a preponderant role of Neu-1 activity for the correct deposition and assembly of elastic fibers. Consequently, Neu-1 appears as a key enzyme in the assembly of elastic fibers.

Elastin Receptor Complex-associated Neuraminidase-1: molecular sensor of elastic fibers degradation

Besides its involvement in elastin and elastic fibers biosynthesis [28], accumulative data from the last decade have shown that ERC and especially Neu-1 also serve as a functional sensor for elastic fiber degradation. Elastic fiber degradation occurs in different pathophysiological contexts and constitutes a typical hallmark of aging and associated diseases. Through EBP engagement, Neu-1 plays a critical role in the signal processes and biological activities mediated by these degradation products. This has been mainly demonstrated for elastin-derived peptides (EDP) [14, 17, 32-36] in the field of cardiovascular diseases [8, 37, 38], cancer progression [4] and emphysema [39, 40]. Signaling events involve mainly the phosphoinositide-3-kinase γ (PI3K γ) pathway and converge to ERK1/2 and Akt activation [41-43] (Figure 2).

Identification and functional characterization of EDP released after elastin degradation have been extensively studied from the pioneer works of Senior *et al.* [44], and the discovery of the first EDP having biological activity towards fibroblasts

and monocytes, the GxxPG-containing peptide VGVAPG. This hexapeptide is located in the central region of the human tropoelastin polypeptide sequence, where it is repeated six times in the domain encoded by exon 24. To date, VGVAPG is considered as the archetypal EDP. Other tropoelastin-derived GxxPG sequences were further identified as bioactive such as PGAIPG [45], GVAPG and GLVPG [46], GVYPG, GFGPG, and GVLPG [47]. Moreover, longer bioactive peptides have also been identified [48]. Theoretical and experimental results concerning VGVAPG and other GxxPG peptides have demonstrated that these intrinsically disordered peptides can transiently sample the type VIII β -turn conformation that is required for their binding to EBP and their biological activities [49-51]. Molecular simulations have proposed that any residues located before this motif increases the β -turn stabilization, but they are not required for biological functions. The residue located after GxxP has no significant structural effect meaning that in the GxxPG bioactive motif, this glycine only has an importance for EBP anchoring and not for the EDPs structural behavior. Moreover, the "x" amino acids found in the GxxPG motif are of importance for obtaining the type VIII β -turn conformation. When $x = G$ at any of these positions, the peptides fail to fold in type VIII β -turn. Additionally, a proline residue located at the first "x" position stabilize the type VIII β -turn structure whereas it blocks the establishment of this conformation when located at the second "x" position [52].

Although elastin is the ECM protein containing the largest number of GxxPG sequences, many other ECM proteins and proteins involved in the constitution of elastic fibers contain such a sequence. For instance, fibrillin-1, -2, and -3, EMILIN-1 and -2, fibronectin, and type III, IV, V, VII, and VIII collagens include at least three GxxPG motifs in their polypeptide sequences [53]. In this context, a fibrillin-1

fragment containing the EGFEPG sequence has been shown to upregulate MMP-1 expression in fibroblasts [53] and to be chemotactic for macrophages [54]. Blocking the interaction between EBP and GxxPG motifs using the BA4 monoclonal antibody [55] or causing shedding of EBP by lactose [56, 57] inhibit chemotaxis to this fibrillin-1 fragment as well as to aortic extracts of mgR/mgR mice, a mouse model of Marfan syndrome associated with increased susceptibility to fragmentation of elastin and fibrillin-rich microfibrils [54]. Importantly, the same group further showed that this monoclonal antibody BA4 can also decrease disease progression and ameliorate manifestations of aortic disease in this mouse model [58].

Although a sialidase inhibitor was not tested in the above-cited works, these data argue for a critical sensor role of Neu-1 *via* EBP engagement during elastic fibers degradation and suggest that specific inhibitors of Neu-1 should be of great value to prevent or decrease the biological effects mediated by these degradation products. Although significant advances have been achieved in the search for Neu-1 inhibitors by using analogs of the broad spectrum sialidase inhibitor 2-deoxy-2,3-didehydro-N-acetylneuraminic acid (DANA) [59], identification of more selective inhibitors of membrane Neu-1 sialidase activity is hampered by our poor knowledge on Neu-1 structure and membrane topology. In the absence of crystallographic data, homology models of the mammalian sialidase family have been developed based on the crystal structure of Neu-2 [60], with Neu-1 being predicted to have the typical structure of sialidases: a β -propeller composed of four anti-parallel β -sheets organized in six blades. However, recent studies on Neu-1 [61] and Neu-3 [62], the second plasma membrane sialidase, rather suggest that these sialidases have the characteristics of an integral membrane protein. By combining molecular biology and biochemical analyses with structural biophysics and computational approaches, two

regions were identified in Neu-1 as potential transmembrane (TM) domains, with its N- and C-termini oriented towards the cytosol. In membrane mimicking environments, the corresponding peptides form stable α -helices and one of these two TM domains is suited for self-association. Interestingly, introduction of point mutations within this TM domain blocks Neu-1 dimerization and decreases membrane sialidase activity [61]. Discovery of such dimer organization opens interesting prospects on ERC stoichiometry at the plasma membrane. Another interesting issue relies on how binding of GxxPG motifs to EBP triggers Neu-1 sialidase activity at the plasma membrane. It is tempting to speculate that the binding of GxxPG motifs to EBP leads to conformational changes within Neu-1 dimers that may help in increasing its catalytic activity. Further clarification on how Neu-1 is inserted within the plasma membrane, together with EBP and PPCA, is required to better understand the regulatory mechanisms of Neu-1 at the molecular level and its participation in biological processes.

Finally, Neu-1 now emerges as a critical regulator of the sialylation level of a myriad of membrane receptors, such as integrins [63, 64], tyrosine kinases receptors [32, 65, 66], Toll-like receptors [67, 68], and more recently CD36 [33]. Desialylation of these receptors by Neu-1 has been shown to modulate their activation and related signaling pathways. Moreover, recent findings have also reported that plasma membrane Neu-1, in complex with MMP-9, G protein-coupled receptors, and tyrosine kinase receptors or Toll-like receptors, could be involved in receptor transactivation [69, 70]. This opens new avenues in the complexity of the biological processes mediated by Neu-1, and possibly by elastic fibers degradation through EBP engagement. Taken together, these data clearly position Neu-1 as a fundamental

molecular sensor of elastic fibers degradation but also as a central regulator of the plasma membrane proteome.

Neuraminidases and elastic fibers remodeling: an unconsidered role for Neu-1 ?

As described above, Neu-1 plays a key role in elastic fibers assembly and degradation sensing. Interestingly, this sialidase belongs to a large family of enzymes conserved through evolution and this point could bring important information about unconsidered roles for Neu-1.

Neuraminidases, or sialidases, are found in several species such as viruses, bacteria, protozoans, birds and mammals [71]. Neuraminidases play a key role in the catabolism of sialoglycoconjugates by cleaving their SA residues to induce temporal changes in their structure and functions [72, 73]. SA, distributed ubiquitously in mammals tissues, are N- or O-substituted derivatives of neuraminic acid (a monosaccharide with a nine-carbon backbone) and their presence in glycoconjugates can modify their functions and interactions with other molecules [74]. These compounds constitute terminal residues on glycan chains of glycoproteins and glycolipids on all living cells. Desialylation of glycoproteins and glycolipids is a crucial mechanism regulating molecular recognitions inside cells, between cells, between the cells and the ECM and between the cells and several pathogens [75].

Interestingly, viruses, bacteria or protozoans use these processes in order to get biological advantage. In this way, the relation between neuraminidases expression and TGF- β release and activation is of great interest. TGF- β is a cytokine which regulates several cellular and immunological processes such as initiation and

resolution of inflammatory responses [76-78]. TGF- β is secreted by cells as a biologically inactive molecule called latent TGF- β (LTGF- β) [79, 80]. This latent complex is composed of the N-terminal latency-associated peptide (LAP) and the mature TGF- β domain which are non-covalently linked [81]. Sha *et al.* have shown that the LAP amino acid sequence 50-85 (including amino acids which are glycosylated and contain terminal SA residues) are essential to LTGF- β complex formation and function [82]. Another form of TGF- β storage involves LTBPs that were identified as forming latent complexes with TGF- β by covalently binding LAP *via* disulfide bonds. Consequently, it has been proposed that LAP, TGF- β , and LTBP form the large latent complex (LLC). Agents that are able to activate LTGF- β induce the dissociation of LAP with the mature domain either by denaturing LAP or by altering its folding, which is a key step in TGF- β function [19, 81].

Several pathogens such as bacteria, parasites or viruses are able to evade immune responses by regulating TGF- β activation. Carlson *et al.* showed that neuraminidases of influenza A viruses and *Clostridium perfringens* activate LTGF- β by removing SA motifs from LTGF- β [19]. Their results have also demonstrated that TGF- β plays a crucial role in the protection of the host from influenza pathogenesis. Strikingly, human Neu-1 presents high sequence similarity and substrate specificity with viruses and bacteria neuraminidases [83, 84]. It could consequently be speculated that the ERC-associated Neu-1 could also participate in the regulation of the bioavailability of TGF- β , suggesting a totally unconsidered role for Neu-1 (Figure 3). Thus, in addition to the well-described role of Neu-1 in elastic fibers assembly and degradation sensing, Neu-1 could also have a pivotal role in the remodelling of

elastic fibers through a potential function in TGF- β release. Of course, this hypothetical new role for Neu-1 remains to be demonstrated.

This hypothesis could also have an importance in pathologies associated with elastic fibers degradation and TGF- β release such as Marfan syndrome (MFS). Marfan syndrome (MFS) is an inherited, autosomal dominant disorder caused by mutations in the fibrillin-1 encoding gene (*FBN1*) with prominent skeletal abnormalities and clinical manifestations in eye, skin and the cardiovascular system [85]. MFS is associated with extensive elastic fibers degradation and excessive TGF- β release [86, 87] due to the inability of fibrillin-1 to restrict TGF- β activation. It could consequently be tempting to speculate that the large amount of GxxPG fragments produced in MFS may also affect such processes by increasing the activation of the ERC and enhancing TGF- β release and activation by the sialidase activity of its Neu-1 subunit.

Conclusion

Elastic fibers are fundamental components of the ECM. They provide, *via* elastin and to a lesser extent through their microfibrils component, elastic recoil to tissues such as skin, arteries or lungs. It is fascinating that their whole life could be seen via the scope of a single enzyme, Neu-1. Indeed, this sialidase plays a key role in their biosynthesis but also has the ability to sense their degradation through the ERC. Finally, interesting data emerging from the sialidase family could lead to the definition of new roles for Neu-1 that could modify the way we consider the regulation of TGF- β bioavailability.

In conclusion, the data summarized here clearly demonstrate that Neu-1 has now to be seen as a crucial regulator of the biochemistry and biology of ECM elastic fibers, opening new ways to consider ECM biology.

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Author contributions

A.B., B.R-C, S.B, M.L., R.G.E. and P.M. performed bibliographic search, summarized and analysed the content of the selected manuscripts. They prepared the figures and revised the edited version. L.M. revised the edited version. L.D. designed the sections and organization of the original outline. He performed bibliographic search and analyzed the content of the selected manuscripts. He edited the original draft and reviewed the final version of the manuscript.

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Figures Legends

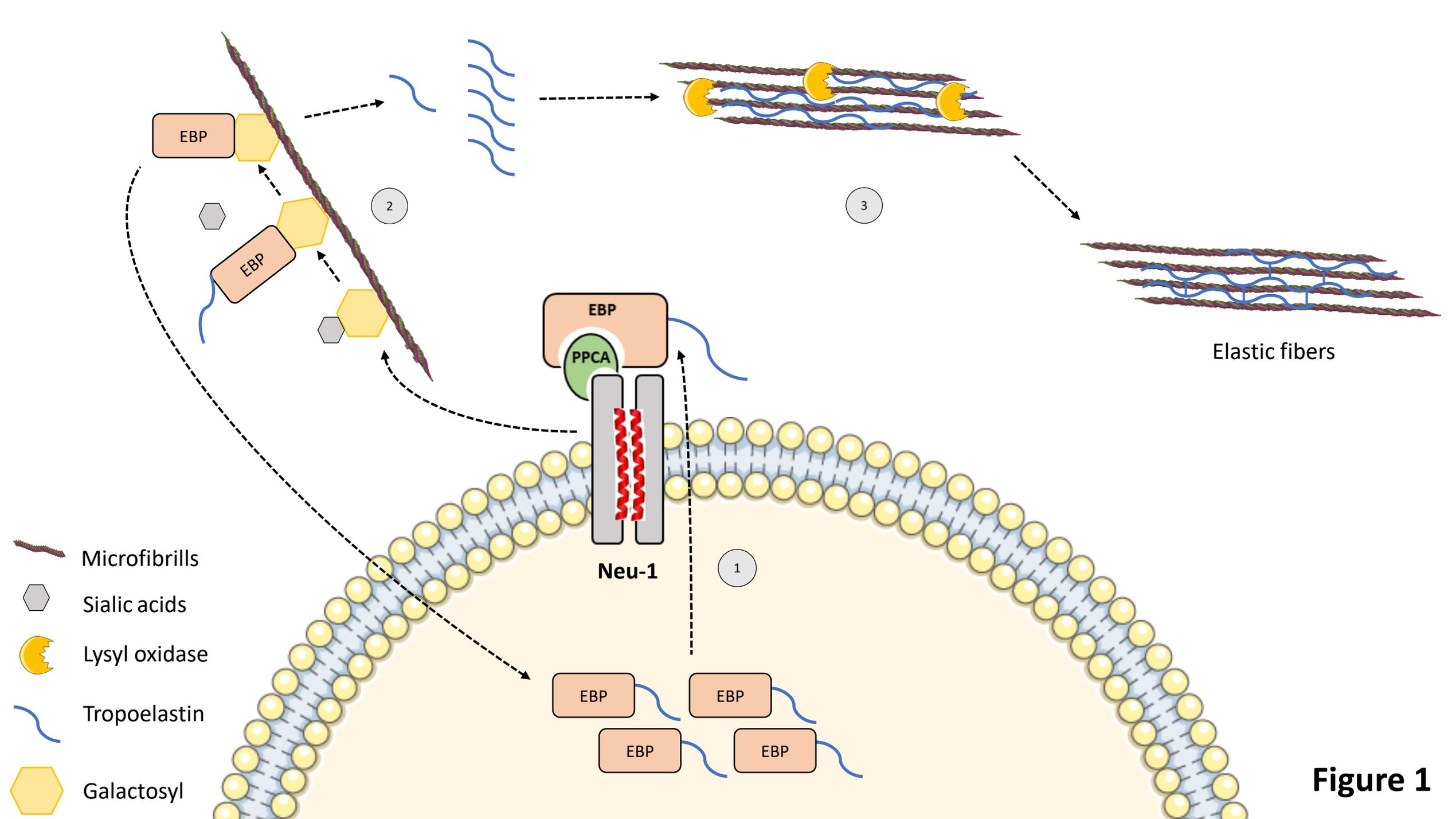
Figure 1: Role of ERC in elastogenesis. 1) After its synthesis, tropoelastin associates with EBP that acts as a chaperone protein accompanying the elastin monomer to the surface of the plasma membrane where it associates with the rest of the ERC, PPCA and Neu-1. 2) The consequent triggering of Neu-1 sialidase activity leads to the desialylation of microfibrillar proteins. The unmasking of galactosyl moieties permits the interaction with EBP leading to the release of tropoelastin and to the recycling of EBP. 3) Tropoelastin is incorporated to the elastic fibers under construction and through lysyl oxidase action, formation of cross-links leads to the formation of mature elastin.

Figure 2: The sensor role of Neu-1 in elastic fibers degradation. Degradation of elastic fibers releases GxxPG fragments from the microfibrils and the elastin core. Binding of GxxPG fragments to the ERC triggers signaling pathways through Neu-1 that involve critical signaling proteins, such as PI3K γ , and converge to ERK1/2 and Akt activation. In addition, Neu-1 modulates the sialylation level and signaling of membrane receptors, such as the insulin receptor [32] and CD36 [33] that also contributes to the biological activities of GxxPG fragments. EBP, elastin-binding protein; ERC, elastin receptor complex, ERK1/2 extracellular-regulated protein kinases 1/2; Neu-1, neuraminidase-1; PI3K, phosphoinositide 3-kinase; PPCA, protective protein/cathepsin A.

Figure 3 : Putative role of Neu-1 as a crucial regulator of TGF- β release.

A) Bacteria, parasites or viruses have been shown to be able to regulate TGF- β activation. Neuraminidases of such organisms (as influenza A viruses and *Clostridium perfringens*) activate LTGF- β by removing sialic acids from LTGF- β and increase

TGF- β bioavailability. B). Hypothesis of a Neu-1-dependent TGF- β activation. Neu-1 presents high sequence similitude and substrate specificity with viral and bacterial neuraminidases. Consequently, it could be postulated that the ERC-associated Neu-1 may also play a role in the regulation of TGF- β bioavailability. In this hypothesis, the ERC is activated by EDP following elastic fibers degradation. The resulting increase in Neu-1 activity leads to the desialylation of LTGF- β resulting in an increase of TGF- β activation.



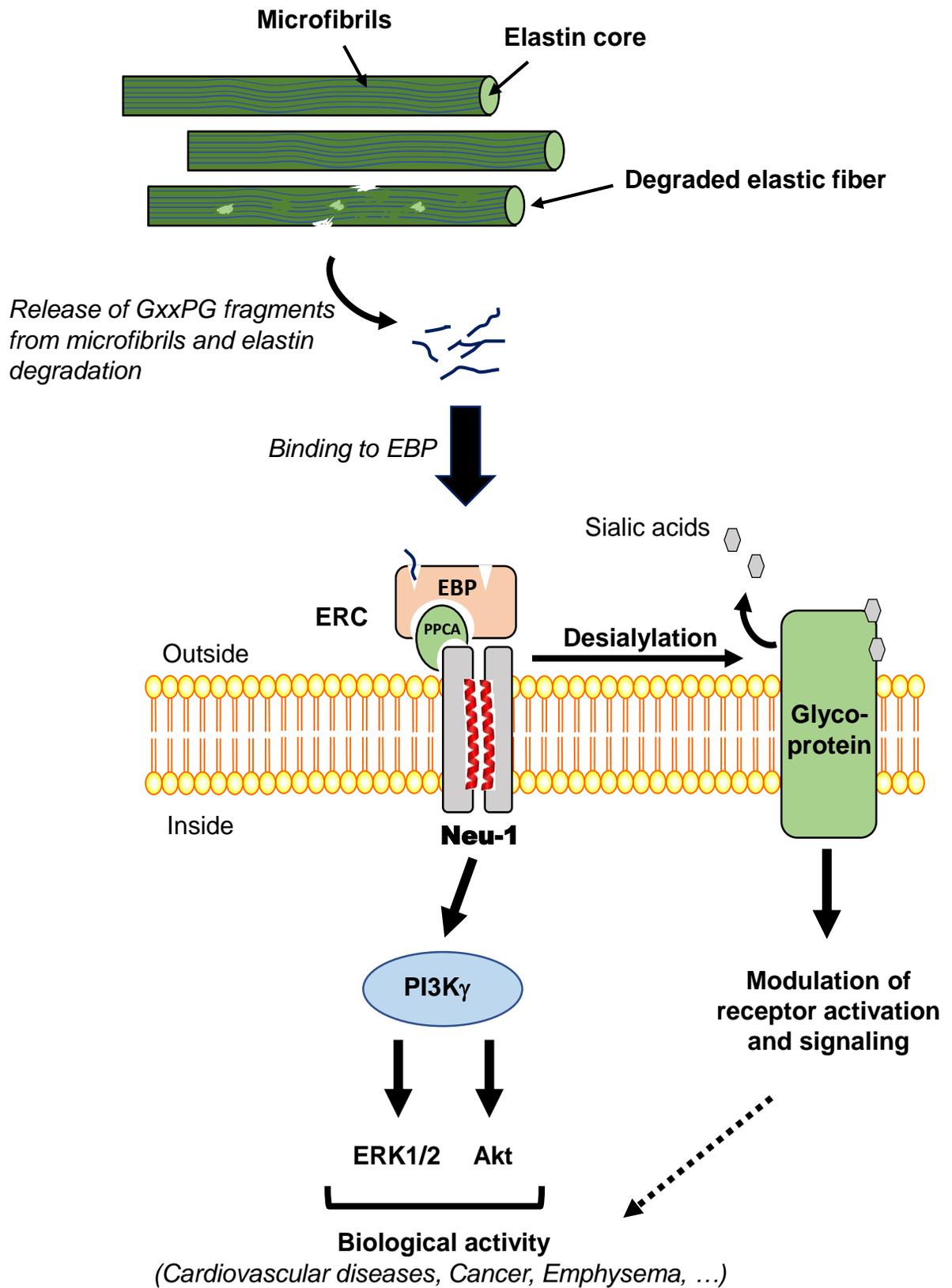
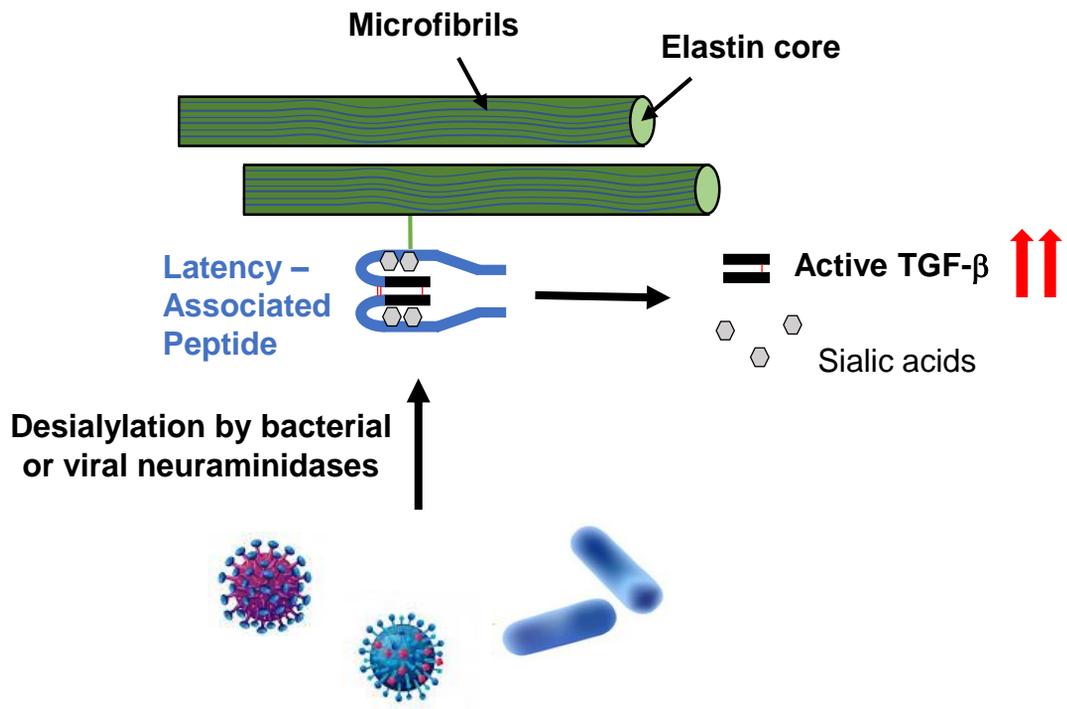
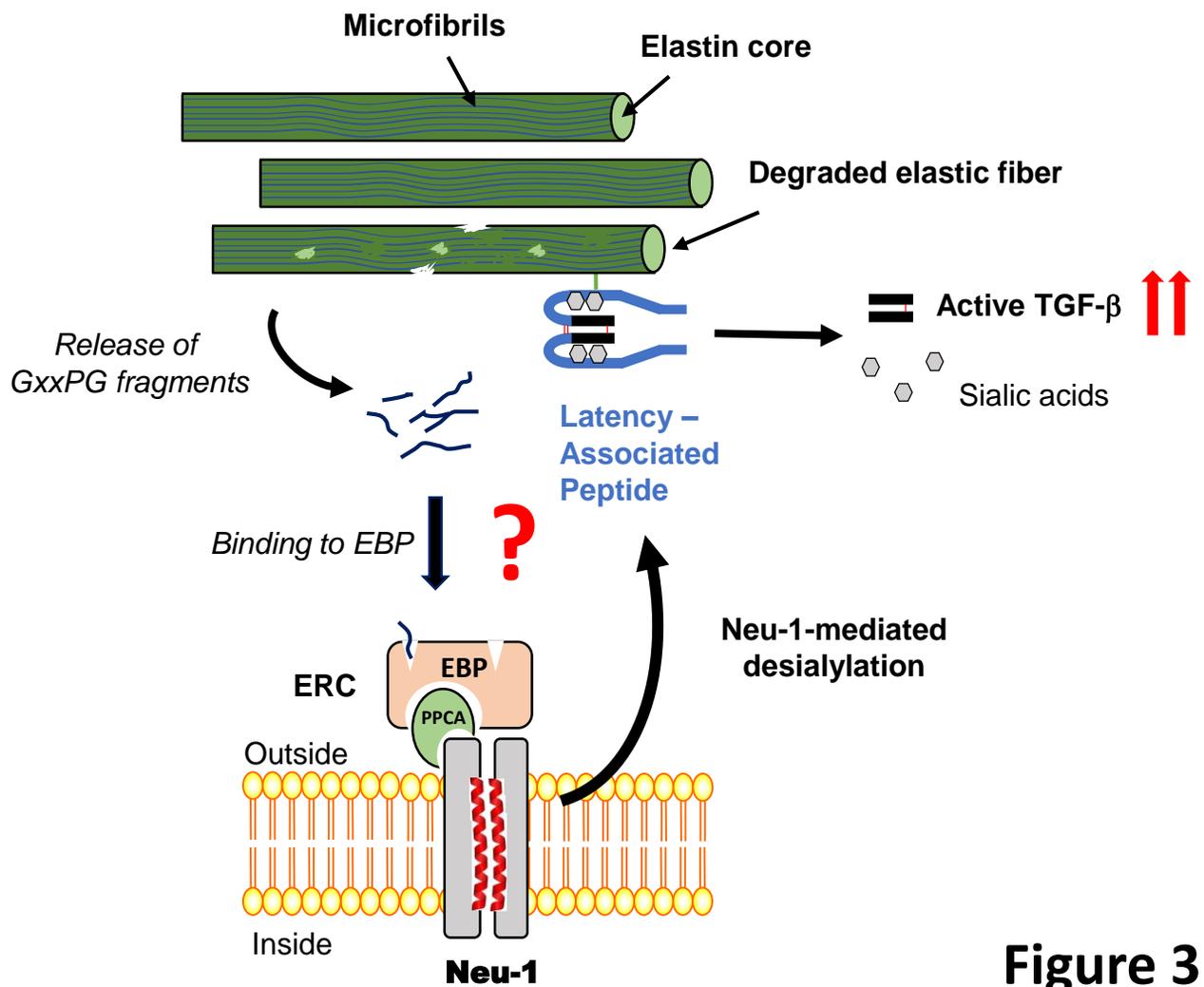


Figure 2

A**B****Figure 3**