A virological view of tenascin-C in infection

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Abstract

Tenascin-C is a large extracellular matrix glycoprotein with complex, not yet fully unveiled roles. Its context- and structure-dependent modus operandi renders tenascin-C a puzzling protein. Since its discovery ~40 years ago, research into tenascin-C biology continues to reveal novel functions, the most recent of all being its immunomodulatory activity, especially its role in infection, which is just now beginning to emerge. Here, we explore the role for tenascin-C in the immune response to viruses, including SARS-CoV-2 and HIV-1. Recently, tenascin-C has emerged as a biomarker of disease severity during COVID-19 and other viral infections and we highlight relevant RNA-Seq and proteomic analyses that suggest a correlation between tenascin-C levels and disease severity. Finally, we ask what the function of this protein during viral replication is and propose tenascin-C as an intercellular signal of inflammation shuttled to distal sites via exosomes, a player in the repair and remodeling of infected and damaged tissues during severe infectious disease as well as a ligand for specific pathogens with distinct implications for the host.

Introduction

Tenascin-C is a large extracellular matrix (ECM) glycoprotein with a characteristic six□armed structure or hexabrachion in which two tenascin-C trimers are joined together. Each arm of the haxabrachion represents a monomer which radiates outwards like the spoke of a wheel and has a multimodular structure (Fig. 1). This structure comprises a N-terminal assembly (TA) domain, which allows trimerization, followed by 14.5 epidermal growth factor (EGF)-like repeats, which contain six cysteine residues involved in intrachain disulfide bonds, up to 17 fibronectin-type III (FNIII) repeats, which can be alternatively spliced giving rise to large and small variants, and a C-terminal fibrinogen-like globe homologous to the β- and γ-chains of fibrinogen (Fig. 1).

Tenascin-C is a promiscuous protein that can bind to many different ligands and, through these interactions, it regulates tissue architecture and homeostasis as well as cell phenotype and function. Ligands encompass cell surface receptors, including multiple integrins(1), EGF-receptor(2) and Toll-like receptor 4 (TLR4)(3) and soluble factors like Wnt/wingless 3a (Wnt3a)(4). Tenascin-C has also been shown to bind to several growth factors such as vascular endothelial growth factor (VEGF), latency-associated peptide (LAP)-TGF-β complex and transforming growth factor beta (TGFβ)(5, 6). Moreover, tenascin-C is able to bind to other ECM molecules, with fibronectin being the best characterized binding partner(7). These molecular interactions allow not only direct tenascin-C-cell interactions, but also impact the ability of soluble factors and ECM molecules to signal to cells, in addition to influencing the structure of the cellular environment. Notably, tenascin-C establishes interactions also with pathogens (i.e. HIV-1 and bacteria), and these will be discussed later.

While tenascin-C is expressed at high levels during development in the embryo(8), its expression in healthy adult tissues is largely confined to the bone marrow, thymus, spleen and lymph nodes where it supports immune cell proliferation, differentiation and function(9). However, tenascin-C is specifically and rapidly induced at sites of tissue injury and infection(10). Increased tenascin-C protein levels are reported in human tumors(11, 12) and sustained expression of tenascin-C is seen in chronic inflammation, with the inflamed joint of rheumatoid arthritis patients representing one of the most investigated pro-inflammatory niches where tenascin-C drives inflammation. Mechanistically, tenascin-C leads to the synthesis of the proinflammatory cytokines TNFα, IL-6 and IL-8 and chemokines such as CCL2, CCL4 and CXCL5 by activating TLR4(3, 13) and integrin α9β1(13), respectively. In the adaptive immune system, tenascin-C has been shown to play a role in the polarization of Th17 lymphocytes in a murine model of inflammatory arthritis(14). Furthermore, tenascin-C can fine-tune the inflammatory response as demonstrated in LPS-activated bone marrow-derived macrophages

and in a murine model of systemic inflammation where it regulated the biosynthesis of miR-155, a very early inflammatory response gene which enhances pro-inflammatory cytokine production(15).

A recent phylogenetic analysis shows that the first tenascin-C coevolved with immunoglobulin-based adaptive immunity together with C-C chemokines, the major histocompatibility complex, T-cell receptors, Toll-like receptor 4 and integrin α9β1(16). This, combined with the spiraling body of evidence that tenascin-C plays an important role in mediating and regulating inflammation, points to a fundamental role for tenascin-C in immunity. In this minireview, we will examine the role of tenascin-C in the immune response to viral infection, a novel and burgeoning area in tenascin-C biology.

Tenascin-C as a biomarker of disease severity during COVID-19 and other viral infections

SARS-CoV-2 infections have resulted in >6 million deaths worldwide, making COVID-19 the deadliest disease outbreak in recent history(17). The clinical outcomes of COVID-19 vary significantly from asymptomatic infection to severe disease characterized by acute respiratory distress syndrome (ARDS) and organ failure. These severe forms of disease are accompanied by an exacerbated inflammatory response, causing a hyper-inflammatory “cytokine storm”(18, 19). The detection of IL-6, TNFα, IL-8 and CXCL10 in peripheral blood are considered hallmarks of these phenomenon that in conjunction with diminished type I and type III interferons, marked lymphopenia, immune exhaustion and dysfunctional myeloid populations, create the perfect environment to promote viral replication, widespread tissue damage and increased mortality risk(20–28).

In the lungs, a specialized ECM not only provides structural support, which allows for air exchange, but also tissue-specific signals that regulate the differentiation, activation, function and proliferation of cells, including infiltrating immune cells(29, 30). Structurally, this ECM is assembled into i) a thin basement membrane, composed of collagen type IV, laminins and proteoglycans, which lines the basal side of epithelia and endothelia and surrounds muscle, fat and peripheral nerve cells; and ii) an interstitial matrix, which is a fibril-like meshwork that maintains the three-dimensional (3D) integrity and biomechanical properties of the lungs by interconnecting the different cell types that reside therein (31) (Fig. 2). Both ECM structures serve as tissue-specific “niches” that regulate the stemness and differentiation of progenitor and stem cells, and the function of tissue-specific differentiated cell types(32). The major components of the lung interstitial matrix are collagens, predominantly type I and III, but also type II, V and XI, all fibrillar collagens which provide high tensile strength, contributing to the architecture of the lung(33). Further, elastic fibers, which are composed of an inner core made of the ECM protein elastin and an outer periphery containing microfibrils made of the glycoproteins fibrillin-1, -2 and -3, microfibril-associated glycoproteins, including fibulins, elastin microfibril interface-located proteins (EMILINs) and members of the elastin-crosslinking lysyl oxidase (LOX) family, confer high elasticity which is vital for the compliance and elastic recoil of lungs(34). In addition to fibrous collagens and glycoproteins, proteoglycans such as perlecan, agrin, decorin, biglycan and lumican are major constituents of the ECM that contribute to its viscoelasticity due to their high hydrophilicity(35). Other ECM molecules, including hyaluronan, fibronectin, and tenascin-C are also present in the interstitial matrix (33)(Fig. 2). For a more detailed dissection of the lung ECM, the reader is referred to two excellent reviews by Burgstaller *et al*. (37) and Zhou *et al*.(38).

Following infection with SARS-CoV-2 virus, the concerted action of immune cells infiltrating the lungs and cytokines leads to overexpression and activation of ECM proteases such as matrix

metalloproteinases (MMPs) that cause ECM breakdown and, potentially, generation of ECM bioactive fragments such as galectin-9 and osteopontin truncated forms, which are significantly elevated in COVID-19 patients associated with pneumonia and, in contrast to their full-length parent proteins, correlate with laboratory markers for lung infection, inflammation, coagulopathy, and kidney function in those patients(39). Detection of fibronectin by proteomic analysis during SARS-CoV-2 infection in plasma samples from COVID-19 survivors compared to healthy control subjects(40) suggests that excessive deposition of ECM molecules could be a hallmark of COVID-19. Such modifications of the lung microenvironment may promote further immune cell infiltration and tissue damage.

Longitudinal proteomic analysis of blood samples from COVID-19 patients showed an increase in tenascin-C levels in blood as disease progressed towards a more severe form. Tenascin-C appeared at the top 17% of most up-regulated proteins in serum with strong association with disease severity and poor prognosis(41). Other studies performing RNA-Seq and high-resolution mass-spectrometry of serum samples found up-regulation of tenascin-C in severe COVID-19 patients compared to non-hospitalized infected individuals(42), and similar increased levels were detected in bronchoalveolar lavage fluid (BALF) from critical COVID-19 patients(43). As tenascin-C is one of the most highly elevated proteins in peripheral blood, it has been proposed as a biomarker for disease progression and severity(42, 43). Interestingly, tenascin-C levels were also significantly up-regulated in blood from non-COVID ARDS hospitalized patients suggesting an association with severe lung injury and disease. A mouse model of SARS-CoV-2 infection using a mouse-adapted strain recapitulated the features observed during COVID-19 in humans where up-regulation of profibrotic genes, including tenascin-C, was found in older mice at later time points (more than 30 day) after viral clearance, correlating with post-acute sequelae of SARS-CoV-2. These signatures were particularly associated with alveolar damage, collagen deposition and extracellular matrix reorganization(44).

Concordantly, tenascin-C has been shown to be highly expressed in many chronic lung inflammatory diseases including bronchopulmonary dysplasia (BPD), chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF), and asthma, where it has been considered as a marker of severity(45–49). Other acute severe respiratory infections, including Influenza A, lead to expression of tenascin-C in BALF and serum(50), further suggesting a correlation with disease worsening (Fig. 3). Furthermore, increased plasma tenascin-C concentrations have been reported in patients with sepsis(51–53). In contrast, mild respiratory infections, including the common cold viruses respiratory syncytial virus (RSV) and human parainfluenza virus (HPIV), do not lead to the upregulation of tenascin-C levels(54). Beyond respiratory tract infections, tenascin-C has also been proposed as a biomarker of chronic hepatitis C infection, as it has been found to be elevated in serum and histological liver samples correlating with active infection, cirrhosis and tissue injury(55, 56), as well as liver fibrosis status(57).

What is the function of tenascin-C in viral infection?

Intercellular signaling

Recently, exosome-mediated secretion of tenascin-C has been shown to occur after its biosynthesis in the endoplasmic reticulum, in a caveolin-1-dependent manner(58). Analysis of serum-derived exosomes from COVID-19 patients identified tenascin-C as one of the most enriched proteins, being >200 fold up-regulated in comparison with exosomes from healthy individuals(59) (Fig. 3). Exosomes are secreted vesicles involved in intercellular communication as they transport bioactive lipids, nucleic acids, metabolites and proteins, playing an important role in disease initiation and development. These tenascin-C-enriched exosomes were shown to induce the expression of TNFα, IL-6 and CCL5 in immortalized hepatocytes via activation of NF-kB signaling. We could hypothesize that tenascin-C signals inflammatory cues to distant organs

and contributes to the cytokine storm in COVID-19(59) (Fig. 3). A follow up study demonstrated that COVID-19-isolated exosomes trigger the activation of the NLRP3 inflammasome in endothelial cells leading to caspase-1 cleavage and release of IL-1β(60) (Fig. 3). This cytokine is also elevated during severe COVID-19 in serum(61) and we could speculate that tenascin-C may contribute to its expression via the activation of NF-kB through TLR4. Similarly, rhinovirus infection or direct stimulation of RNA sensing pathways by the synthetic double-stranded RNA poly(I:C) leads to the expression of soluble tenascin-C as well as exosomes rich in this protein, which was particularly enhanced in primary bronchial epithelial cells from atopic asthmatic patients(62). These exosomes were also able to stimulate inflammatory gene expression in macrophages and bronchial lung epithelial cells. Furthermore, this study showed that the C-terminal FBG domain of tenascin-C can induce the expression of IL-8 in lung epithelial cells suggesting that cytokine expression is a result of the activation of TLR4 by this domain(62).

Tissue remodelling and repair

Mechanistically, it is still unclear what is inducing tenascin-C expression during SARS-CoV-2 infection: is it produced by infected cells or is it induced as a consequence of tissue damage? Single-cell RNA-Seq analysis of cellular phenotypes in the nasal mucosa of SARS-CoV-2 infected patients revealed that tenascin-C levels are up-regulated in basal cells of the nasal epithelium, which are not the target of infection(63). These are precursor cells that are capable of differentiating into secretory, goblet and ciliated cells. During severe SARS-CoV-2 infection, a dramatic loss of mature ciliated cells is observed in nasal swabs that is associated with secretory cell expansion and differentiation, and the accumulation of deuterosomal cells and precursor cell intermediates, suggesting the activation of a compensatory repopulation of the damaged ciliated epithelium(63). Similarly, single-cell analysis from autopsy specimens found abundant tenascin-C levels in inflamed alveoli compared to normal alveoli in COVID-19 patients. In the lung, this protein is induced mainly by tumor protein p63 (TP63+) intrapulmonary

basal-like progenitor (IPBLP) cells(64), which have been shown to act as a reservoir for the regeneration of damaged alveoli after lung injury and in influenza H1N1 mouse models of infection(65, 66). This result suggests that tenascin-C could be induced as a consequence of tissue damage playing an important role in tissue remodelling and repair during severe lung injury. In addition, tenascin-C has been associated with pathway enrichment analyses including wound healing, extracellular structure organization, response to wounding and negative regulation of cell adhesion(64).

Conversely, the tenascin-X member of the tenascin family is significantly downregulated in COVID-19 patient sera compared to healthy controls(67), as well as in lung tissue as a result of remodelling and destruction of ECM components that occurs during COVID-19 progression(68). These findings are recapitulated in a humanized animal model of SARS-CoV-2 infection, where tenascin-X levels are significantly downregulated in the lung 2 days post-infection(69). As SARS-CoV-2 cannot infect mice, these humanized mouse models represent relevant systems to study lung and immune human responses during infection *in vivo*(70, 71). The pattern of tenascin-X expression in SARS-CoV-2 infection is opposite to that of tenascin-C, and it is not surprising if we consider that this is also the case in embryonic and adult tissues(72), and frequently in disease such as cancer where an antagonistic role for tenascin-X and tenascin-C has been proposed(73, 74). Nevertheless, decreased protein levels of tenascin-X could simply be the result of ECM breakdown and tissue remodelling that occur during SARS-CoV-2 infection.

Tenascin-C-virus interaction

It has also been demonstrated that tenascin-C is highly abundant in breast milk, where it is able to block HIV-1 infection(75). More than 90% of HIV-1 exposed breastfed infants will escape getting infected (76), and tenascin-C was identified as an important contributor to protection

against HIV (Fig. 4). Tenascin-C can neutralize a wide variety of HIV-1 strains including transmitter founder clones, and both CCR5 and CXCR4 tropic variants(75). Strikingly, tenascin-C is able to bind directly to HIV virions and capture them to the same level as monoclonal targeting HIV-envelope antibodies(75).

Mechanistic studies revealed that both long and short isoforms of tenascin-C binds to HIV-1 Env with a Kd of ~54-58 nM, and that tenascin-C oligomerization is fundamental for virus neutralization, suggesting that multiple arms of tenascin-C work in coordination to inhibit multiple regions of HIV-1 Env or multiple Env on the virion surface(77) (Fig. 4). Specifically, tenascin-C neutralization capacity is exerted by the FBG and FNIII domains, which interact with the V3 loop region of the HIV-1 Env. In addition, it was shown that the Env amino acids 321/322 and 326/327 are essential for tenascin-C binding(77).

Tenascin-C levels in breast milk varied between 2.2 and 671 ug/mL, which is aligned with the IC_{50} concentration needed to neutralize different HIV-1 variants (100-150 ug/mL)(75). In contrast, very little tenascin-C is detected in mucosal fluids (<0.1 ug/mL), including semen and cervicovaginal lavage, demonstrating that these amounts are not sufficient to inhibit HIV-1 transmission(78). However, recombinant tenascin-C has been shown to effectively neutralize HIV in comparison to breast milk-isolated tenascin-C, and thus, its exogenous administration has been proposed as a potential therapeutic avenue to prevent HIV transmission post-natally and sexually(78).

Discussion

The ECM plays a fundamental role during viral infection, where it serves as a scaffold for tissue repair, cell signaling, immune responses and viral clearance. Tenascin-C is one of these ECM proteins that is heavily involved in activating inflammatory pathways and tissue remodeling

during viral replication, and it has also been proposed to modulate infection outcomes by direct interaction with pathogens.

While HIV-1 is the only virus currently known to establish a direct physical interaction with tenascin-C, other pathogen-tenascin-C interactions have been reported. In human breast milk, tenascin-C could interact with Staphylococcal superantigen-like protein 8 via its fibronectin (FN) type III repeats 1–5 and this inhibited the binding of tenascin-C to fibronectin, attenuating keratinocyte motility and delaying wound closure *in vitro(79)*. Specific *Streptococcus gallolyticus* strains, the causative agents of infective endocarditis, were shown to adhere to purified, immobilized full-length tenascin-C, an important factor for the infection of host tissues(80, 81). Protein H-expressing *Streptococcus pyogenes* bacteria could also establish protein-protein interactions with tenascin-C via its FNIII domains (FN1 and FN3), in a RGD-independent manner(82). Understanding these interactions may help define the mechanisms which lead to viral-bacterial superinfections such as those caused by Influenza A virus (IAV) and *S. pyogenes* (the group A Streptococcus; GAS). A recent study shows that IAV infection of A549 cells increases tenascin-C expression which may enhance bacterial colonization and disease severity given the ability of GAS to bind to immobilized and A549 cell expressed tenascin-C, largely via its Protein F2 (PrtF.2)(50). The importance of dissecting tenascin-C-pathogen interaction is underscored by the current development of biologics which target *Staphylococcus aureus* virulence factors, which are used by the pathogen to subvert the host immune response. Specifically, centyrins, small protein scaffolds derived from the fibronectin type III–binding domain of tenascin-C, are being tested *in vivo* for their ability to bind to *S. aureus* leukocidins with high affinity and protect primary human immune cells from toxin-mediated cytolysis(83).

Another area of current study is the role of exosomes rich in tenascin-C as drivers of cell communication of inflammatory insults. Exosomes are largely induced during viral and parasitic

311 infection playing important roles in immune modulation, pathogen genetic transfer and infection,
312 and movement of cargo effectors to distant sites(84–86). This system has the advantage of
313 transporting proteins like tenascin-C to sites beyond local protein expression to signal injury at
314 distal places in the body and modulate immune responses towards viral infection. For example,
315 RSV infected cells produced exosomes capable of inducing the expression of cytokines and
316 chemokines in macrophages and epithelial cells(87). How this process is regulated and what
317 are the consequences of tenascin-C expression during chronic viral infection where persistent
318 inflammation is detrimental for viral clearance is still a subject of investigation.
319
320 Another open question is what factors drive tenascin-C expression during viral replication. One
321 hypothesis is that tenascin-C is induced directly after viral detection in infected cells. Mills *et al.*
322 showed that tenascin-C can be expressed and released after poly(I:C) stimulation of lung
323 epithelial cells(62). Poly(I:C) mimics double stranded viral RNA, triggering the RNA sensors
324 RIG-I, MDA5 and/or TLR3, leading to the activation of the NF-kB pathway that could induce the
325 expression of tenascin-C. However, in this study the up-regulation of tenasicn-C occurred 48
326 hours after stimulation suggesting that it might be produced indirectly by the secretion of factors
327 that increase tenascin-C expression. For example, tenascin-C is induced by TNFα or other
328 cytokines that are also expressed downstream of these RNA receptors, and incremental
329 amounts of tenascin-C are detected in cell supernatants 48 and 72 hours after poly(I:C)
330 treatment(62).
331
332 An important factor in the antiviral response is the production of type-I and type-III interferon that
333 effectively restricts viral infection. Interestingly, a study by Lebensztejn *et al.(88)* has shown that
334 interferon alpha treatment suppresses tenascin-C expression. This could be due to suppression
335 of viral replication or antagonism of cytokines like TNFα by type-I interferons(89). On the
336 contrary, treatment of bronchial epithelial cells with TNFα and interferon gamma significantly

increased the expression of tenascin-C *in vitro(90)*. These studies highlight the complex interplay between these pathways and the need to dissect how the expression of ECM proteins like tenascin-C is regulated during infection to better understand their beneficial or detrimental role during resolution of viral replication.

Finally, in severe respiratory infections such as COVID-19, there is a combination of impared interferon responses and imbalanced innate immune activation characterized by delayed interferon expression and high levels of pro-inflammatory cytokines like TNFα and IL-6, which could promote the expression of tenascin-C. This is in contrast to mild respiratory infections, where the type-I interferon response is adequate to clear viral infection. Moreover, in mouse models and in humans infected with SARS-CoV-2, lung fibrosis is a key feature of long COVID and disease severity and it is mainly driven by the expression of TGFβ(44, 91). This cytokine is a major inducer of tenascin-C and could be the main factor contributing to tenascin-C expression during chronic and severe COVID-19. TGFβ induces the expression of tenascin-C during embryogenesis and injury contributing to tissue remodeling(92, 93). This is in line with tenascin-C pattern of expression during SARS-CoV-2 infection, where it is associated with sites of tissue repair and regeneration of damaged epithelium and alveoli. Moreover, it has been suggested that tenascin-C is a paramount factor for the development of TGFβ induced fibrosis after lung injury(94). This evidence fuels the hypothesis that tenascin-C expression is induced by this key cytokine to initiate tissue repair and remodeling as in embryogenesis. However, this phenomenon is impaired due to the continuous secretion of multiple cytokines and tissue damage leading to long term sequelaes as observed in long-COVID patients. Notably, most studies looking at broad host responses after viral infection using omics approaches only serve to correlate levels of tenascin-C expression with disease phenotype. Therefore, loss and gain of function validation of the proposed roles for tenascin-C as well as mechanistic studies revealing

the mode of action and signaling modulation by this protein during viral replication are imperative(95).

Overall, these studies demonstrate the significance of understanding the function and consequences of tenascin-C expression and interactions during viral-driven inflammation, where it is considered a biomarker for disease severity, but it can also be targeted to alleviate excessive inflammatory responses and tissue damage, and even directly modulate viral entry and replication.

Figure legends

Figure 1. Morphology and multimodular structure of tenascin-C.

The hexameric structure of tenascin-C protein is shown. Each monomer consists of an assembly domain (black), 14.5 epidermal growth factor (EGF)-like repeats (blue), 17 fibronectin-type III (FNIII) repeats, including 8 constant FNIII repeats (purple) and 9 alternatively spliced FNIII repeats (white), and a fibrinogen-like globe (cyan). Integrin α9β1 and TLR4, two receptors mediating the proinflammatory activity of tenascin-C, and TGF-β and latency-associated peptide (LAP)-TGF-β complex, two ligands potentially involved in the function of tenascin-C in SARS-CoV-2 infection, are shown in orange next to the relevant interacting domain.

Figure 2. Overview of the lungs and their extracellular matrix structure and composition.

The basic structure of healthy lungs is shown. This includes the main airways or bronchi that divide into smaller branches which terminate into air sacs or alveoli. The two main structures of

387 the lung ECM, namely the basement membrane and the interstitial matrix, and their location
388 within the lung are schematically represented together with their major components.
389
390 **Figure 3. Tenascin-C expression and function in severe respiratory infections.**
391 Tenascin-C expression is not induced during mild respiratory infections, including those caused
392 by the common cold viruses respiratory syncytial virus (RSV) and human parainfluenza virus
393 (HPIV). In contrast, Influenza A and SARS-CoV-2 induce tenascin-C expression with amounts
394 correlating with disease severity. In the lung, this protein is synthesized mainly by TP63+
395 intrapulmonary basal-like progenitor (IPBLP) cells, which help regenerate damaged alveoli,
396 suggesting a potential role for tenascin-C in the repair and remodeling of the damaged lung.
397 High levels of tenascin-C are not only found in serum and bronchoalveolar lavage fluid (BALF)
398 from COVID-19 critically ill patients, but also in their serum-derived exosomes. *In vitro*
399 experiments suggest that these exosomes allow tenascin-C to exert its inflammatory activity at
400 distant sites such as the liver and endothelial cells through activation of NF-kB and the NLRP3
401 inflammasome, respectively.
402
403 **Figure 4. Antiviral function of tenascin-C in HIV-1 infection.**
404 In the mammary gland, mammary epithelial cells synthesize and secrete tenascin-C in human
405 breast milk(96, 97). In milk, oligomeric tenascin-C prevents transmission of HIV-1 to breastfed
406 infants likely by directly interacting with the virions. The interaction takes place between the
407 FBG and FNIII domains of tenascin-C and the V3 loop region of the HIV-1 Env.
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Author contributions

L.Z.A. and A.M.P. conceived and designed the research; A.M.P. prepared the figures; L.Z.A. and A.M.P. drafted, edited, and revised the manuscript, and read and approved the final version of the manuscript.

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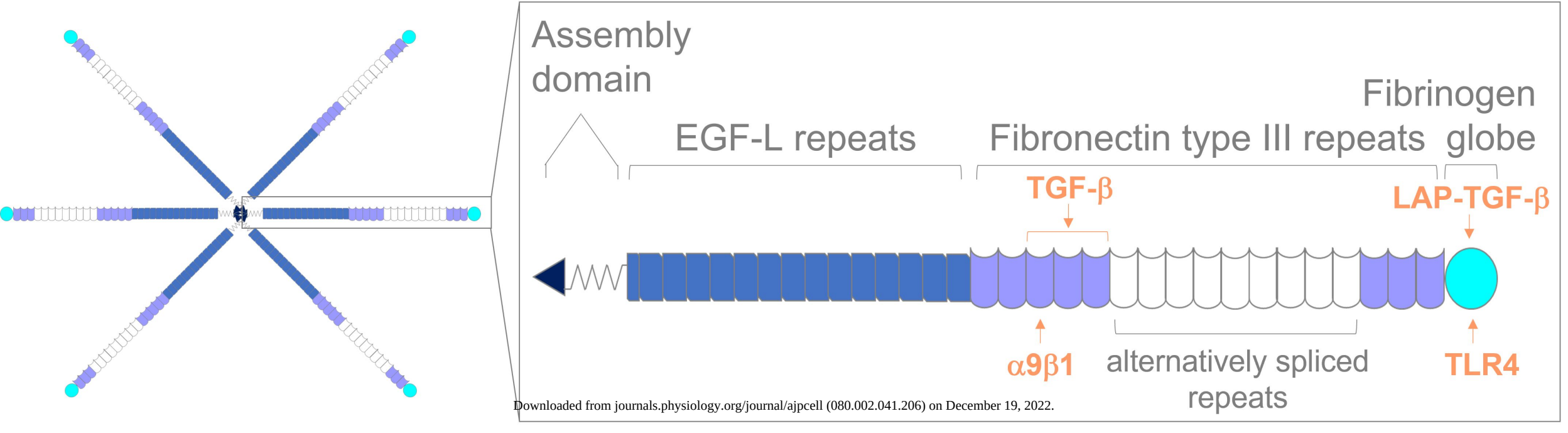
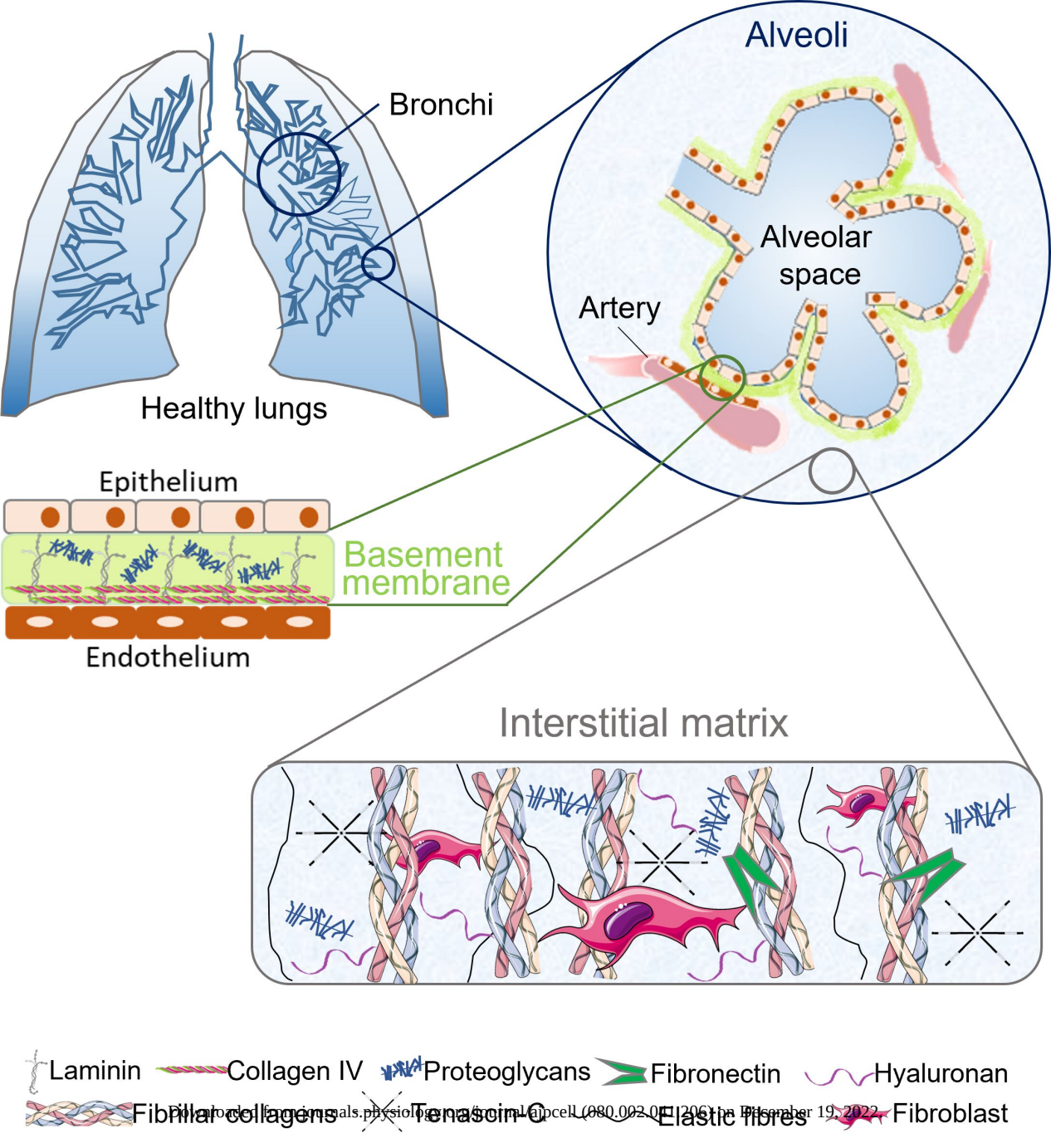
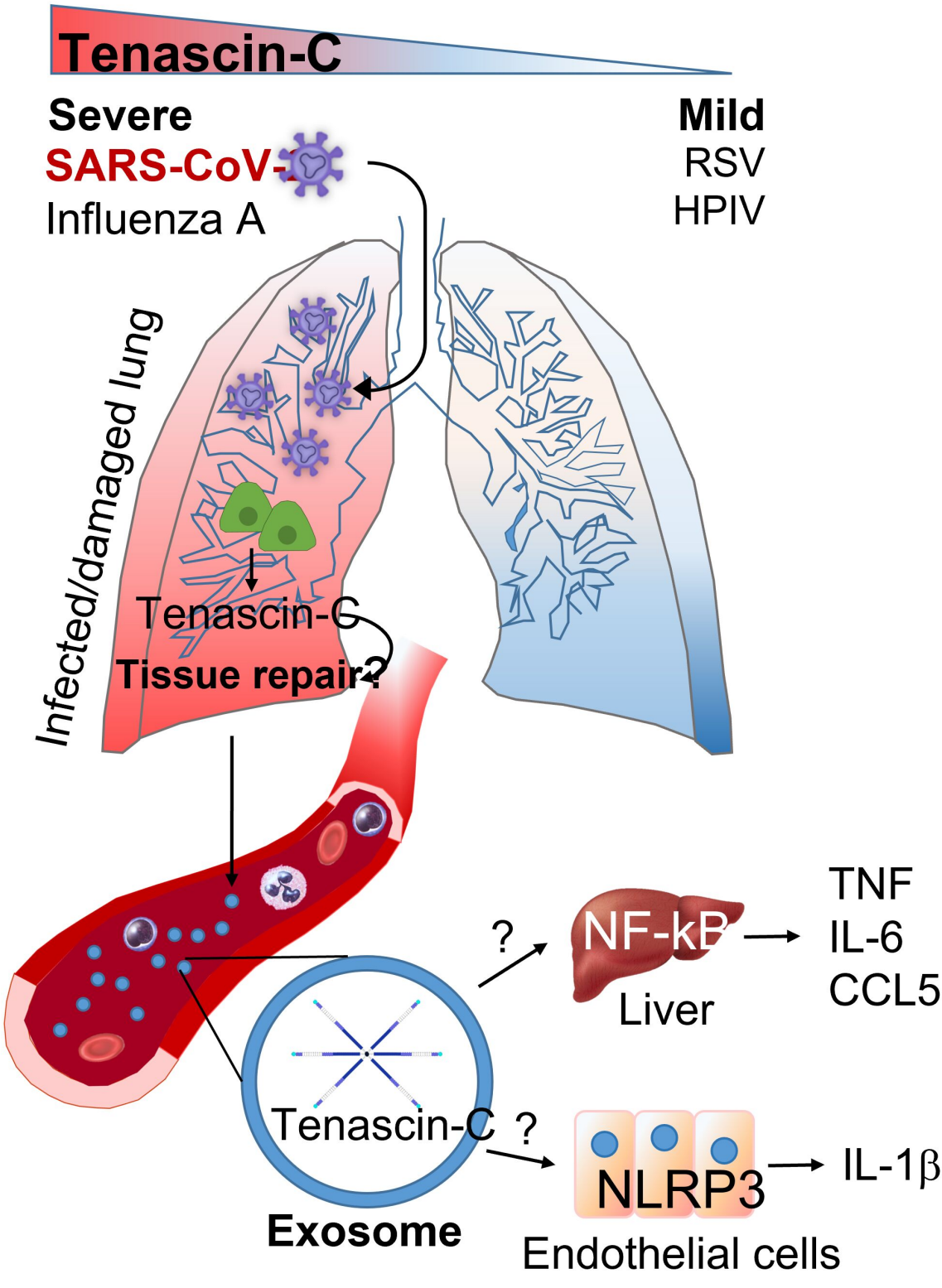
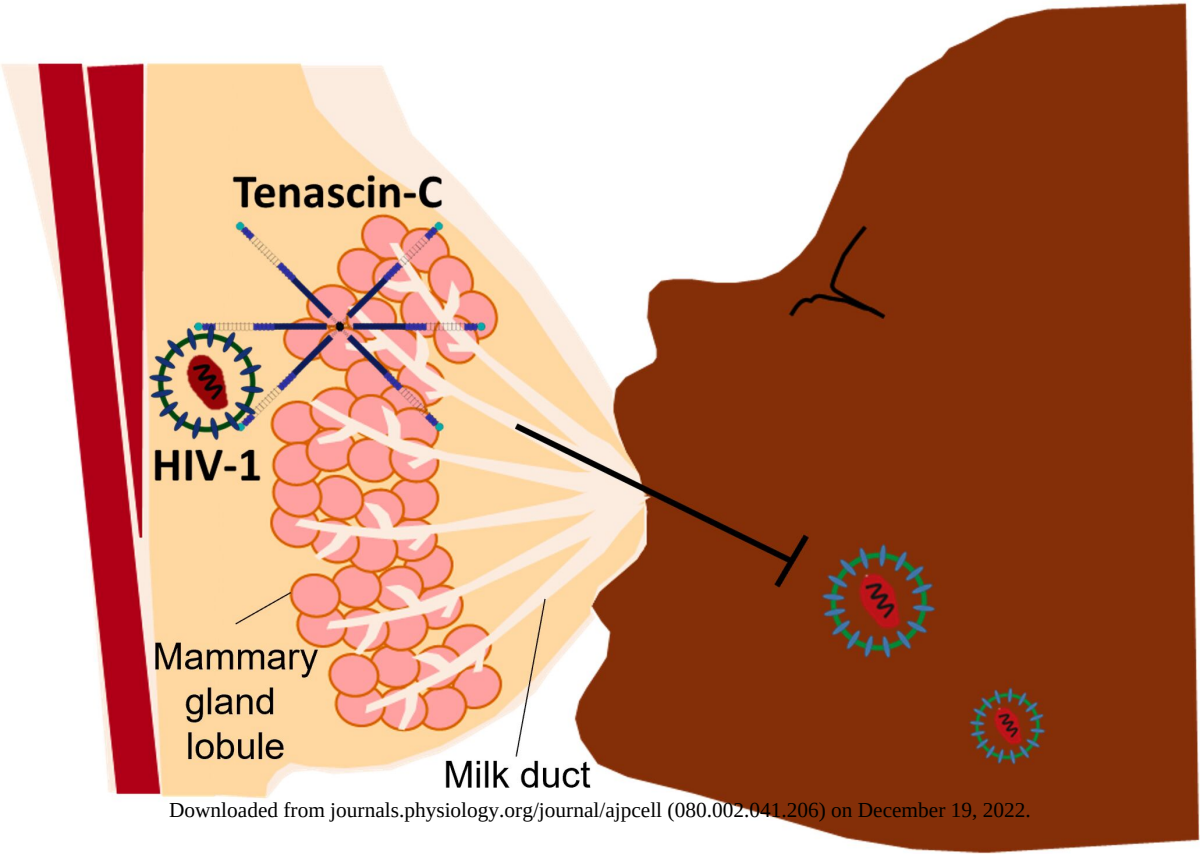




Lung infection



HIV-1 infection

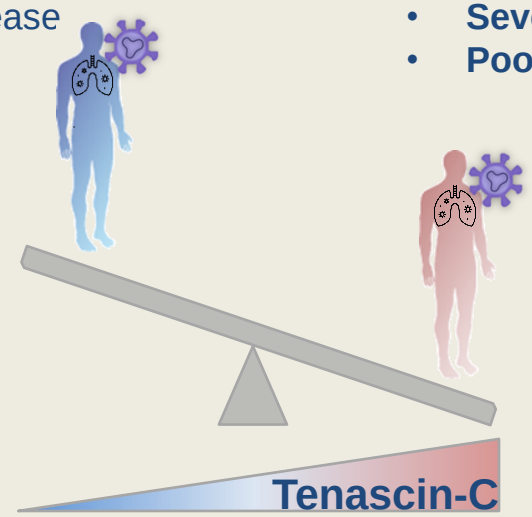


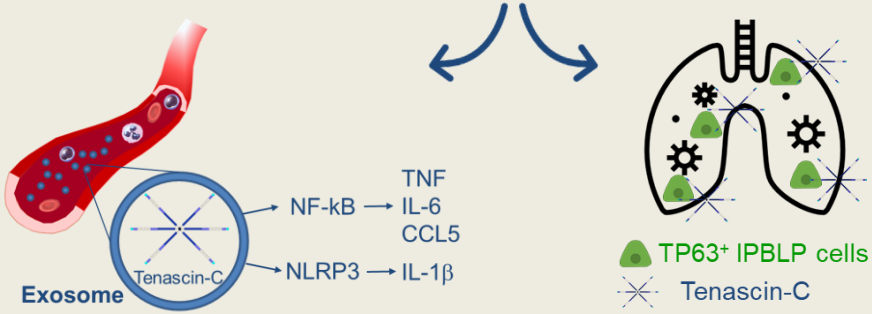
Tenascin-C in viral infection

SARS-Cov-2

- Mild disease
- Survival

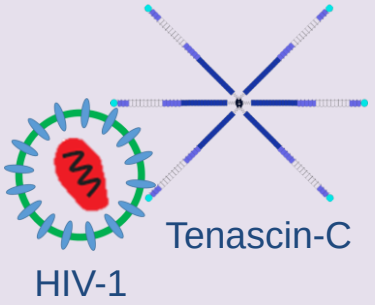
- **Severe disease**
- **Poor prognosis**



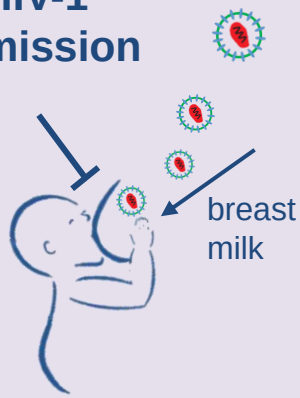


Inflammation? **Tissue repair?**

HIV-1 virus neutralization



Prevention of HIV-1 transmission



Tenascin-C interacts with HIV-1