

## ● PERSPECTIVE

## Neurodegenerative diseases are a function of matrix breakdown: how to rebuild extracellular matrix and intracellular matrix

**Matrix within cells, the cytoskeleton, and that which surrounds cells, the extracellular matrix (ECM), are connected to one another through a number of receptors including those in primary cilia, serving as an important chemical and physical signaling system:** Mechanical forces generated through the matrix play a critical role in determining the form and function of tissues (Hughes et al., 2018). Such forces, even in adult tissues, will be important given that breakdown of the ECM in adults may lead to the tissue changing from an adult phenotype to one of primordial or embryonic (Bhat and Bissell, 2014). As an example, chemical and mechanical signaling from the microenvironment and ECM to the cell can be so powerful as to change cellular phenotype from one of cancer to a normal somatic form (Bhat and Bissell, 2014). Even in development and inheritance, the matrix is important for what embryos receive from egg and sperm upon fertilization. Centrioles, the matrix structures responsible for cell division, are given by the paternal gamete. In the oocytes, the maternal gametes, the centriole is lost through desolvation. Thus, paternal matrix inheritance through the centriole structure is another important example of mechanism of heredity beyond the genome that may have consequences to neural dysfunction.

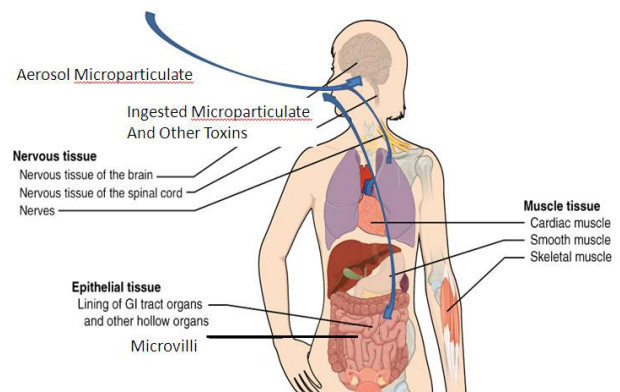
Although the cilium is a relatively small structure its importance as a structural and chemical bridge between intracellular and extracellular compartments is large. For example, the ciliary membrane is the obligate site of action for receptors of a number of signaling systems that profoundly condition cell growth, morphology, and adhesion, and is a specialized site of action for additional signaling receptors. Cilia arise from most cell types, including neural stem cells where the cilia are involved in the cell's transition from quiescence (Khatri et al., 2014). Wang and Barr (2016) have proposed that the cilium is a dedicated organelle for extracellular vesicle (EV) biogenesis and EV reception. The basal body and its associated transition-fiber proteins are thought to regulate protein entry and exit from the cilia compartment, including the release of exosomes (Wang and Barr, 2016). Cilia connecting with the ECM, through expression of integrins and NG2 on primary cilia, help to determine the morphology and adhesion properties, and other phenotypes of the cell (Seeger-Nukpezah and Golemis, 2012) (**Figure 1**).

Breakdown of matrix occurs in neurological diseases, including amyotrophic lateral sclerosis (Maguire and Maguire, 2018). The breakdown of matrix includes the perineuronal nets, a condensed form of ECM that surrounds many types of neurons, especially those with high spike rates, such as retinal ganglion cells and motor neurons. Breakdown of the primary cilia can lead to altered integrin function, ECM, and matrix metalloproteinase (MMP) activity, as well as fibrotic scarring, thought to be a major barrier to central nervous system (CNS) regeneration (Fernández-Klett and Priller, 2014). Fibrosis is a double edge sword during the repair of nervous system in the adult, providing mechanisms that are both positive and negative in the process of neural regeneration (**Figure 2**).

**Breakdown of matrix occurs through a number of environmental regulators:** Including one's exposome (Rappaport, 2016; Maguire, 2017). As the ECM breakdowns through environmental insult, the chemical and mechanical signals and connections of the primary cilia to the ECM will be modified, resulting in an intracellular matrix change. Having lost a normal microenvironment, the result could be that the cell senses a more primordial state, and therefore changes phenotype to one where developmental and embryonic circuits are activated in search of a new identity (Bhat and Bissell, 2014). Furthermore, loss of a normal microenvironment and ECM will mean that neurons no longer receive their normal complement of heat shock protein (HSP) and chaperone proteins from surrounding neural stem cells (Maguire, 2017). In such cases, protein misfolding results and prion-like seeding and spreading of the misfolded proteins occurs. This is a major mechanism underlying neurodegeneration, and does

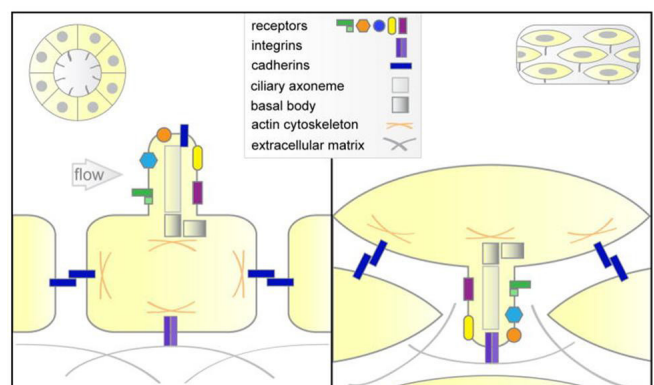
not involve the genome (Maguire and Maguire, 2018).

**Reparation of matrix is accomplished using a combination of stem cell released molecules (S2RM), amino acids, and prebiotics, probiotics, and postbiotics:** Because many neurological diseases are a function of proteinopathies, proteostatic renormalization is particularly useful to quelling the disease state. Indeed, proteinopathy will activate microglia and the onset of the neuroinflammatory cascade (Chakrabarty et al., 2015). Such activation is important, for example, in the clearance of amyloid proteins in Alzheimer's disease (AD) models. However, we can imagine that ECM breakdown, when occurring chronically because of aging and exposome insult (Rappaport, 2016), will lead to an interruption of proteostasis and an onset of the disruption of immunoproteo-



**Figure 1** Early onset of matrix breakdown throughout the body in neurodegenerative diseases.

In some cell and tissue types, as in renal tubules, cilia protrude into lumens (left panel), while in others, such as neural tissue, cilia extend towards the extracellular matrix (ECM) (right panel). Multiple receptors for soluble growth factors or for mechanosensory stimuli (e.g., fluid flow) localize to the ciliary membrane, controlling signaling cascades that influence cell proliferation, polarity, and interaction with the ECM. Some canonical cell adhesion receptors, including cadherins, and integrins, have been shown to be themselves localized to the cilium in some cell types. Some basal body-localized proteins with ciliary functions also regulate the actin cytoskeleton (Seeger-Nukpezah and Golemis, 2012).



**Figure 2** Types of cilia in lumen and extracellular matrix.

In neurodegenerative diseases, early onset mechanisms underlying the disease include matrix breakdown and gut dysbiosis and leaky gut syndrome. Matrix breakdown occurs in the extracellular matrix and perineuronal net surrounding neurons and the neuromuscular junction, as well in the intestines. Matrix breakdown also occurs intracellularly in neuronal cilia, and the microvilli of the intestine. Matrix breakdown may occur through the exposome as microparticulate and other toxins enter the body through the nasal vasculature, lungs, and the gut. The consequences of matrix breakdown include phenotypic changes in neurons and other cell types, and an inability of chaperone proteins and heat shock protein to repair misfolded proteins leading to the prion-like spreading of the malformed proteins within the nervous system.

stasis. (Chakrabarty et al., 2015). Therefore without proteostasis, such as in the case of an overabundance of the anti-inflammatory cytokine interleukin (IL)-10 for example and an under abundance of proinflammatory cytokines, IL-6 for example, neurodegenerative processes may be triggered (Chakrabarty et al., 2015). In astronomy the Goldilocks principle is that planets must revolve about a star in a habitable zone where conditions are suitable for life. In neurodegeneration we may therefore think about a Goldilocks zone where protein content, both pro-inflammatory and anti-inflammatory, is normalized so that ECM and immune related proteins, including chaperones and HSPs, and those responsible for autophagy, are maintained in a zone suitable for life.

Stem cells and progenitor cells, such as fibroblasts, are responsible for building the ECM through the secretion of the necessary molecules to build the biochemical scaffold, as well as other proteins, such as HSPs and chaperone proteins that are required for normal neural function. As such, stem cell released molecules (SRM) as a therapeutic are a key means to rebuild ECM and provide the other proteins, such as chaperones and HSP, required for normal protein folding and neural function (Maguire, 2017). Many of the proteins and other molecules necessary for neural repair are packaged into exosomes (Maguire, 2017) that may be released through the control by the stem cell's cilia (Wang and Barr, 2016). Emerging evidence now suggests that the ECM can also be partially built through various molecules, including proteins, tryptophan metabolites, and polysaccharides, released by commensal bacteria in the gut (Ruiz et al., 2014; Maguire and Maguire, 2018). Indeed, ECM that originates from the bacteria in our guts, a form of bacterial biofilm, has been shown to have important health benefits (Ruiz et al., 2014). Therefore rebuilding of the ECM in the gut through the use of commensal bacteria, *i.e.*, probiotics, the molecules that feed these commensal bacteria, *i.e.*, prebiotics, and the molecules that these bacteria release, *i.e.*, postbiotics, is important to the therapeutic regimen for neurological disorders (Maguire and Maguire, 2018). Gut alterations are known to be expressed early, before inflammation or other symptoms are expressed in a number of neurological diseases such as amyotrophic lateral sclerosis (ALS) and Parkinson's disease. Without a normal matrix barrier present in the gut, leaky gut syndrome results and the molecules that bacteria make, including amyloids, along with bacteria themselves, may systemically enter the body and travel into the nervous system. Evidence that bacteria have entered the brain of AD patients has recently been published. Whether the bacteria are causative, or involved in the initial AD sequelae, or whether the bacteria enter the brain later as a result of blood brain barrier disruption is not known.

One additional component in the gut's matrix will be important to neural repair; the microvilli of the intestinal epithelial. Microvilli are covered in plasma membrane, which encloses cytoplasm and microfilaments. Though these are cellular extensions, there are little or no cellular organelles present in the microvilli. Each microvillus has a dense bundle of cross-linked actin filaments, which serves as its structural core, with about 20 to 30 tightly bundled actin filaments are cross-linked by bundling proteins fimbrin (or plastin-1), villin and espin to form the core of the microvilli. Actin filaments, present in the cytosol, are most abundant near the cell surface. These filaments are thought to determine the shape and movement of the plasma membrane. Changes in molecular composition of the cytoskeleton can lead to nucleation and a dramatic change in self-assembly of the microvilli, leading to diminution of the microvilli structure, including the glycocalyx, a pericellular matrix important for nutrient uptake. Consequent reductions in mechanical autophagy and nutrient absorption result (Maguire and Maguire, 2018).

The means to rebuild the microvilli is now understood. In patients and animals treated with ionizing irradiation, gastrointestinal toxicity results within the first week of exposure. Using an amino acid rehydration solution ingested as a supplement, Yin et al. (2016) have demonstrated that the surface area of microvilli in such patients can be increased. Parenthetically, while ionizing irradiation treatment for cancer is known to be associated with brain toxicity, even when the brain is not irradiated, the mechanisms underlying this toxicity have not been studied, and thus we cannot conclude the toxicity results from microvilli disruption. Part of the consequences of irradiation is a reduction in Lgr5 labeled stem cells in the gut, reduced microvilli surface area, leaky gut, induce  $Cl^-$  secretion, and diarrhea (Yin et al., 2016). With a certain amino acid supplement, Yin et al. (2016) were able to significantly ameliorate these symptoms of irradiation. Therefore the amino acid supplement becomes one component of the neurodegeneration remedy proposed here. Also included in the supplement would be molecules that stem and progenitor cells release

that build the ECM and provide chaperone and HSP activities crucial for neural repair, along with prebiotics, probiotics, and postbiotics. These molecules are known to condition the gut, and to absorb into the body (Maguire, 2017) Important dosing parameters have been described by Maguire and Maguire (2018).

In conclusion, I have presented evidence that part of the key early onset of neurodegeneration involves a breakdown of matrix throughout the body, including the ECM and the intracellular matrix, in the nervous system and in the gut. To rebuild the matrix I have laid out a general plan for therapeutic development using a supplement that uses the molecules that stem cells release, along with amino acids and prebiotics, probiotics, and postbiotics that help rebuild the extracellular and intracellular matrix, *i.e.*, the cytoskeleton of the cilia and the villi of the epithelial cells lining the gut.

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Open peer review report:

Reviewer: Jérôme Braudeau, AgenT, France.

Comments to author: This subject is interesting and often unrecognized by neuroscientists. Especially, the potential interaction between brain and gut (and its bacterial fauna) through the extracellular matrix during neurodegenerative disease progression must be kept in mind. Indeed, it's important to apprehend neurodegenerative diseases, especially Alzheimer's disease, as whole body pathology. However, in order to facilitate the reading by non-experts of extracellular matrix, it could be pertinent to simplify secondary information amounts.

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