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Roles of constitutively secreted extracellular chaperones in neuronal cell repair and regeneration

Sandeep Satapathy[1, 2, *], Mark R. Wilson[3, 4]

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From the Contents

Abstract

Protein quality control involves many processes that jointly act to regulate the expression, localization, turnover, and degradation of proteins, and has been highlighted in recent studies as critical to the differentiation of stem cells during regeneration. The roles of constitutively secreted extracellular chaperones in neuronal injury and disease are poorly understood. Extracellular chaperones are multifunctional proteins expressed by many cell types, including those of the nervous system, known to facilitate protein quality control processes. These molecules exert pleiotropic effects and have been implicated as playing important protective roles in a variety of stress conditions, including tissue damage, infections, and local tissue inflammation. This article aims to provide a critical review of what is currently known about the functions of extracellular chaperones in neuronal repair and regeneration and highlight future directions for this important research area. We review what is known of four constitutively secreted extracellular chaperones directly implicated in processes of neuronal damage and repair, including transthyretin, clusterin, α2-macroglobulin, and neuroserpin, and propose that investigation into the effects of these and other extracellular chaperones on neuronal repair and regeneration has the potential to yield valuable new therapies.

Key Words: cell viability; clusterin; extracellular chaperones; inflammation; neuroserpin; protein misfolding; transthyretin; α2-macroglobulin

Introduction

Local tissue inflammation and mechanical injury to neurons have been associated with the aggregation of misfolded proteins and subsequent cell death (Gidalevitz et al., 2011). Relative to mature differentiated cells, regenerating cells have higher rates of protein synthesis (Noormohammadi et al., 2018), and recent studies have highlighted the critical need for effective protein quality control in stem cells during regeneration (Yan et al., 2020). Proteomic studies of human mesenchymal stromal stem cells have also shown that during regeneration, the secretion of a number of constitutively secreted chaperones (e.g. α2-macroglobulin, A2M) is selectively enhanced (Kehl et al., 2019). Constitutively secreted extracellular chaperones (ECs) are an integral part of the systems that act to maintain protein homeostasis (proteostasis) (Yerbury et al., 2007; Wyatt et al., 2013) and are almost certain to influence the ability of an organism to repair and regenerate cells and tissues. An effective protein quality control system ensures the timely recognition, refolding, or clearance of misfolded proteins to enhance the survival and proper functioning of living organisms (den Brave et al., 2021).

Regenerating neurons need to communicate with other neurons and surrounding cells to generate an effective response to a physiological or pathological stimulus, in which both intracellular and extracellular signaling mechanisms play an important role (Liu et al., 2021). Our understanding of the roles of ECs in neuronal regeneration and repair is currently limited. ECs are multifunctional proteins expressed by many cell types in the body (including neurons and astrocytes), known to facilitate extracellular protein quality control processes. We propose that future studies of ECs in the context of neuronal damage and disease have significant potential to lead to the development of valuable new therapies. In this article, we have focussed on four ECs (transthyretin, clusterin, α2-macroglobulin, and neuroserpin) because these proteins are constitutively present in cerebrospinal fluid (CSF) and have been directly implicated in neurodegenerative disease and diseases associated with neuronal damage and repair (Satapathy and Wilson, 2022). We aim to provide a critical review of what is currently known about the functions of ECs in neuronal repair and regeneration and highlight outstanding questions and future directions for this important research area.

Database Search Strategy

The manuscript used peer-reviewed articles chosen from PubMed, PubMed Central, Google Scholar and Web of Science (Clarivate) identified using individual or combinations of the following keywords: Protein misfolding, extracellular chaperones, transthyretin, clusterin, α2-macroglobulin, neuroserpin, inflammation, cell viability. The date of the last database search is between February 20 and March 30, 2022.

Current Knowledge of the Role of Extracellular Chaperones in Neuronal Repair and Regeneration

A major role of chaperones is to protect organisms from the consequences of inappropriate protein aggregation and toxicity. As a result of age or ongoing chemical or physical stresses, proteins can misfold to form aggregates that are either amorphous or amyloid (fibrillar) in structure, some of which are cytotoxic (Gidalevitz et al., 2011; Hidalgo San Jose et al., 2020). ECs have an ATP-independent action and are best-known for their abilities to (a) inhibit the aggregation of misfolded or damaged proteins, (b) maintain aggregating proteins in a soluble state, and (c) form stable complexes with aggregating extracellular proteins to facilitate their clearance from the extracellular space and subsequent safe disposal by intracellular degradation (Wyatt et al., 2011). ECs are abundant in human body fluids such as plasma and CSF (Prikrylova Vranova et al., 2016), saliva (Pallardo-Fernández et al., 2020), urine (Musiał et al., 2020), and semen (Saleh et al., 2020). In addition, these multifunctional proteins have roles that include suppressing inflammation, inhibiting apoptosis, promoting cell proliferation and survival, modulating ECM composition and organization, and acting as immune modulators (Satapathy and Wilson, 2022). Many of the biological functions of ECs outlined above have been proposed to play critical roles in the regeneration of mature cells, including neuronal cells (Guerin et al., 2021). Further investigation into the effects of ECs present in CSF on neuronal repair and regeneration has the potential to lead to the development of new therapies.

Transthyretin

Transthyretin (TTR) is an amyloid-specific EC (West et al., 2021) present at ~15.5 μg/mL in the CSF of healthy human adults (Maetzler et al., 2012). TTR in complex with retinol-binding protein (RBP) transports retinoic acid (RA, a growth factor) to sites of neuronal growth, thereby promoting neuronal regeneration (Vancamp et al., 2019; Eira et al., 2021), differentiation, and patterning under physiological (Wilson et al., 2004) and pathological conditions (Ikeda et al., 2005). RA carried by the TTR:RBP complex also induces the differentiation of neural stem cells into neurons and glial cells (Nonaka et al., 2004).

[1]Blavatnik Institute of Cell Biology, Harvard Medical School, Boston, MA, USA; [2]The Broad Institute of MIT and Harvard, Cambridge, MA, USA; [3]Molecular Horizons and The School of Chemistry and Molecular Bioscience, University of Wollongong, Northfields Avenue, Wollongong, NSW, Australia; [4]Illawarra Health and Medical Research Institute, Northfields Avenue, Wollongong, NSW, Australia

*__Correspondence to:__ Sandeep Satapathy, PhD, ssatapat@broadinstitute.org.

https://orcid.org/0000-0003-1479-1280 (Sandeep Satapathy)

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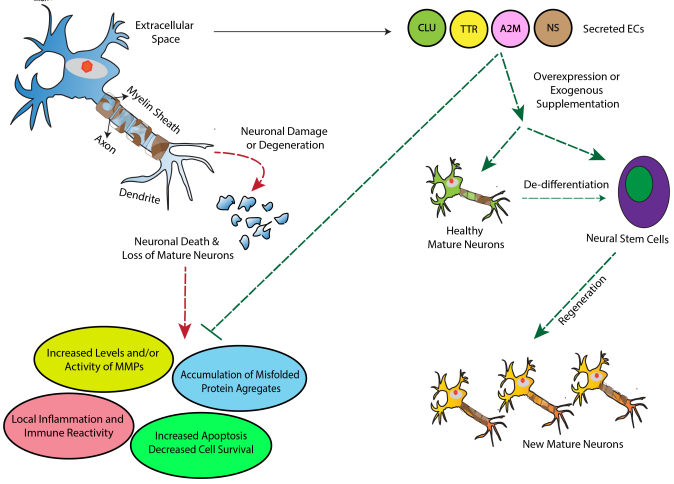

Figure 1 | Proposed model for the roles of ECs in the repair and regeneration of neurons.
Mature neurons (comprising of cell body, axon surrounded by the protective myelin sheath, and dendrites) exhibit cell damage and death following neuronal injury or during neurodegeneration (McGinley et al., 2016; Qian and Zhou, 2020). Neuronal repair and regeneration are inhibited by increased local tissue inflammation, elevated immune reactivity due to increased levels of complement proteins, cell death associated with the presence of reactive astrocytes and glial cells, increased activity of matrix metalloproteinases (MMP), and local accumulation of misfolded protein aggregates in the extracellular space (McGinley et al., 2016; Qian and Zhou, 2020). ECs such as transthyretin (TTR), clusterin (CLU), α2-macroglobulin (A2M), and neuroserpin (NS) are constitutively expressed by neurons under both physiological and pathological conditions and are secreted into the cerebrospinal fluid (CSF) at increased levels in response to neuronal injury and/or neurodegeneration (Satapathy and Wilson, 2022). By inhibiting the accumulation of misfolded proteins, inflammation, MMPs, and apoptosis, the increased expression of ECs is likely to inhibit neuronal injury and/or degeneration and promote neuronal repair and regeneration. Red dashed arrows indicate the biological outcomes of neuronal injury/degeneration. Green dashed lines indicate the biological outcomes of increased levels of ECs (arrowheads indicate a positive effect, the solid line indicates inhibition). ECs: Extracellular chaperones.

TTR has also been suggested to play a cytoprotective role in neurodegeneration and acute neuronal injury cases. A decrease in the level of TTR in the CSF has been associated with Alzheimer's disease (AD; Gião et al., 2021). TTR has been shown to (a) inhibit amyloid (but not amorphous) protein aggregation both *in vitro* (West et al., 2021) and *in vivo* (Schwarzman et al., 1994), (b) proteolytically cleave the amyloid beta peptide *in vitro* (Costa et al., 2008), and (c) rescue a mouse model of AD from cognitive and motor impairment (Buxbaum et al., 2008). TTR has been proposed to facilitate the safe disposal of aggregating proteins from the neuronal extracellular space (Buxbaum et al., 2008; Santos et al., 2010). Similarly, increased CSF TTR levels have been shown to confer cytoprotection against cerebral ischemia (Santos et al., 2010), promote axonal and neurite growth, and facilitate cytoskeletal reorganization following sciatic nerve injury (Eira et al., 2021). Collectively, this preliminary evidence suggests that TTR has the potential to act as a therapeutic agent to reduce inflammation, and promote the survival, repair, and regeneration of neurons.

Clusterin

Clusterin (CLU) is the best-studied EC found at ~2 μg/mL in the CSF of healthy human adults (Polihronis et al., 1993). It has been shown to promote the *in vitro* and *in vivo* proliferation and regeneration of damaged (a) epithelial cells of the cornea (Okada et al., 2011) and intestine (Liu and Chen, 2020), (b) renal cells (Gobe et al., 1995), and (c) hair and cochlear cells (Zhao et al., 2021). CLU inhibits the aggregation of proteins that form either amyloid or amorphous aggregates *in vitro* (West et al., 2021), and has been implicated as performing a cytoprotective role in neurodegenerative diseases and neuronal injuries. For example, increased levels of CLU are detected in the CSF of AD (Nilselid et al., 2006) and Parkinson's disease (PD) patients, and in the conditioned medium of human neuronal (SHSY5Y) (Gregory et al., 2017) and rat primary hippocampal and glial cells (Cascella et al., 2013) that have been exposed to chemical or proteotoxic stress. Rare non-synonymous mutations in the CLU gene are associated with the progression and severity of AD (Bettens et al., 2015) and PD (Ma et al., 2011), and CLU is often found co-localized with amyloid fibrils or plaques surrounding both neurons and glial cells in these diseases (Thambisetty et al., 2010). Furthermore, in mice with transected hypoglossal nerves (a model system for paralysis), reduced levels of CLU in the plasma inhibited the regeneration of sensory neurons (Wicher et al., 2008; Wright et al., 2014).

The cytoprotective role of CLU is further supported by its ability to inhibit (a) local tissue inflammation (Pucci et al., 2019; De Miguel et al., 2021), (b) oxidative stress (Tarquini et al., 2020), and (c) cell death via apoptosis (Cunin et al., 2016). CLU can also influence the composition of the extracellular matrix by inhibiting matrix metalloproteinases MMP9 (Jeong et al., 2012) and MMP25 (Matsuda et al., 2003), and preserving neuronal function at synapses (Chen et al., 2021). All of these findings point toward the potential use of CLU as a therapeutic agent to promote the repair and regeneration of injured neurons.

α2-Macroglobulin

α2-Macroglobulin (A2M) is a broad-range protease-inhibitor and well-studied EC normally present at ~1.5 μg/mL in CSF (Suzuki et al., 2019). A2M inhibits proteases associated with local tissue inflammation and is known to promote the regeneration of (a) stem cells including hematopoietic and lymphopoietic cells in an irradiated mouse model, and (b) mature cells such as retinal epithelial cells (Jaldín-Fincati et al., 2019) and skin epithelial cells, to promote wound healing (Bakhtyar et al., 2018). Similar to CLU, increased levels of A2M have been reported in the CSF of AD (Varma et al., 2017) and PD (Gupta et al., 2019) patients, and correlate with the increased detection of neuronal injury markers such as tau and phosphorylated tau proteins (Varma et al., 2017).

Furthermore, A2M transports inflammatory cytokines (e.g. tumor necrosis factor α and interleukins-6 and -1β; Marino-Puertas et al., 2019), growth factors (e.g. transforming growth factor β; LaMarre et al., 1991) and neurotrophin (a secreted protein that acts as a growth factor and promotes neuronal cell survival and function; Wolf and Gonias, 1994) to sites of tissue inflammation. Therefore, A2M has been suggested to play a key role in suppressing inflammation and promoting neuronal repair and regeneration in neurons subject to mechanical injury (Garcia-Fernandez et al., 2021) or exposure to misfolded protein aggregates (Guan et al., 2021). This trafficking of regulatory molecules may involve the interaction of A2M with the cell surface receptor LRP1 (low-density lipoprotein receptor-related protein-1) (Galliano et al., 2008). A2M also influences extracellular matrix remodeling by inhibiting the protease activity of MMP-2 (Kim et al., 2017) and MMP-9 (Serifova et al., 2020). The A2M-MMP interaction has been suggested to inhibit inflammation and promote the survival of neurons in humans treated with methotrexate (a model for blood-brain barrier damage) (Cucullo et al., 2003). Taken together, the existing evidence supports a role for A2M in enhancing neuronal survival, repair, and regeneration following mechanical injury or neurodegeneration.

Neuroserpin

Neuroserpin (NS) is a constitutively expressed neuronal protein found at relatively low abundance in normal CSF (~7 ng/mL) (Nielsen et al., 2007). NS is a serine protease inhibitor that inhibits the activity of tissue-type plasminogen activator (tPA) (Hastings et al., 1997). Like TTR, NS acts as an amyloid-specific EC (West et al., 2021). Several studies have suggested that NS protects regenerating neurons from injury and neurodegeneration. For example, in a mouse model of cerebral hypoxia, a decrease in the CSF NS level has been suggested to result in an increased expression of tPA in brain neurons, ultimately resulting in neuronal cell death (Tsirka et al., 1995; D'Acunto et al., 2021). Furthermore, in a rat model of stroke, the level of NS protein in brain neurons was significantly increased as early as 6 hours post-stroke and remained high for 1 week after the stroke (Yepes et al., 2000). In the same study, direct injection of NS protein into the brain resulted in a ~64% reduction in the stroke volume when compared with rats injected with a placebo (Yepes et al., 2000). These observations suggest that the cytoprotective potential of NS makes it an attractive candidate for exploration as a therapeutic agent to promote neuronal repair and regeneration.

Concluding Hypothesis and Future Directions

ECs are (i) abundantly found in CSF, and their levels increase following neuronal injury or neurodegenerative stress, and (ii) known to regulate multiple biological processes including those that are important for the repair and regeneration of cells, such as cell proliferation, apoptosis, inflammation, and interactions with the ECM. Based on these observations we propose that ECs are key players in neuronal repair and regeneration and that future studies to better characterize their effects in this specific context has the potential to lead to the development of valuable new therapies for neuronal damage and diseases. We suggest that a focus in future studies on the following outstanding questions in the field would bring us closer to being able to harness the therapeutic potential of ECs to treat neuronal damage and disease:

1. In neuronal culture systems, what are the effects on receptor expression and neuronal cell viability of (i) exogenous supplementation of ECs, and (ii) silencing of the expression of one or multiple ECs using CRISPR-mediated gene editing (Bock et al., 2022)?
2. Is the level of expression of cell surface receptors known to be important in neuronal growth and regeneration (e.g. LRP1, integrins, and neurotrophic receptors) affected by the expression of ECs in injured and healthy neurons?
3. Does the level of expression of ECs affect (a) the expression of other intracellular or secreted proteins known to be important for cell repair and regeneration and/or (b) the differentiation of neural stem cells?

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References

Bakhtyar N, Jeschke MG, Herer E, Sheikholeslam M, Amini-Nik S (2018) Exosomes from acellular Wharton's jelly of the human umbilical cord promotes skin wound healing. Stem Cell Res Ther 9:193.

Bettens K, Vermeulen S, Van Cauwenberghe C, Heeman B, Asselbergh B, Robberecht C, Engelborghs S, Vandenbulcke M, Vandenberghe R, De Deyn PP, Cruts M, Van Broeckhoven C, Sleegers K (2015) Reduced secreted clusterin as a mechanism for Alzheimer-associated CLU mutations. Mol Neurodegener 10:30.

Bock C, Datlinger P, Chardon F, Coelho MA, Dong MB, Lawson KA, Lu T, Maroc L, Norman TM, Song B, Stanley G, Chen S, Garnett M, Li W, Moffat J, Qi LS, Shapiro RS, Shendure J, Weissman JS, Zhuang X (2022) High-content CRISPR screening. Nat Rev Methods Primers 2:8.

Buxbaum JN, Ye Z, Reixach N, Friske L, Levy C, Das P, Golde T, Masliah E, Roberts AR, Bartfai T (2008) Transthyretin protects Alzheimer's mice from the behavioral and biochemical effects of Abeta toxicity. Proc Natl Acad Sci U S A 105:2681-2686.

Cascella R, Conti S, Tatini F, Evangelisti E, Scartabelli T, Casamenti F, Wilson MR, Chiti F, Cecchi C (2013) Extracellular chaperones prevent Abeta42-induced toxicity in rat brains. Biochim Biophys Acta 1832:1217-1226.

Chen F, Swartzlander DB, Ghosh A, Fryer JD, Wang B, Zheng H (2021) Clusterin secreted from astrocyte promotes excitatory synaptic transmission and ameliorates Alzheimer's disease neuropathology. Mol Neurodegener 16:5.

Costa R, Ferreira-da-Silva F, Saraiva MJ, Cardoso I (2008) Transthyretin protects against A-beta peptide toxicity by proteolytic cleavage of the peptide: a mechanism sensitive to the Kunitz protease inhibitor. PLoS One 3:e2899.

Cucullo L, Marchi N, Marroni M, Fazio V, Namura S, Janigro D (2003) Blood-brain barrier damage induces release of alpha2-macroglobulin. Mol Cell Proteomics 2:234-241.

Cunin P, Beauvillain C, Miot C, Augusto JF, Preisser L, Blanchard S, Pignon P, Scotet M, Garo E, Fremaux I, Chevailler A, Subra JF, Blanco P, Wilson MR, Jeannin P, Delneste Y (2016) Clusterin facilitates apoptotic cell clearance and prevents apoptotic cell-induced autoimmune responses. Cell Death Dis 7:e2215.

D'Acunto E, Fra A, Visentin C, Manno M, Ricagno S, Galliciotti G, Miranda E (2021) Neuroserpin: structure, function, physiology and pathology. Cell Mol Life Sci 78:6409-6430.

De Miguel Z, Khoury N, Betley MJ, Lehallier B, Willoughby D, Olsson N, Yang AC, Hahn O, Lu N, Vest RT, Bonanno LN, Yerra L, Zhang L, Saw NL, Fairchild JK, Lee D, Zhang H, McAlpine PL, Contrepois K, Shamloo M, et al. (2021) Exercise plasma boosts memory and dampens brain inflammation via clusterin. Nature 600:494-499.

den Brave F, Gupta A, Becker T (2021) Protein quality control at the mitochondrial surface. Front Cell Dev Biol 9:795685.

Eira J, Magalhaes J, Macedo N, Pero ME, Misgeld T, Sousa MM, Bartolini F, Liz MA (2021) Transthyretin promotes axon growth via regulation of microtubule dynamics and tubulin acetylation. Front Cell Dev Biol 9:747699.

Galliano MF, Toulza E, Jonca N, Gonias SL, Serre G, Guerrin M (2008) Binding of alpha2ML1 to the low density lipoprotein receptor-related protein 1 (LRP1) reveals a new role for LRP1 in the human epidermis. PLoS One 3:e2729.

Garcia-Fernandez P, Uceyler N, Sommer C (2021) From the low-density lipoprotein receptor-related protein 1 to neuropathic pain: a potentially novel target. Pain Rep 6:e898.

Gião T, Saavedra J, Vieira JR, Pinto MT, Arsequell G, Cardoso I (2021) Neuroprotection in early stages of Alzheimer's disease is promoted by transthyretin angiogenic properties. Alzheimers Res Ther 13:143.

Gidalevitz T, Prahlad V, Morimoto RI (2011) The stress of protein misfolding: from single cells to multicellular organisms. Cold Spring Harb Perspect Biol 3:a009704.

Gobe GC, Buttyan R, Wyburn KR, Etheridge MR, Smith PJ (1995) Clusterin expression and apoptosis in tissue remodeling associated with renal regeneration. Kidney Int 47:411-420.

Gregory JM, Whiten DR, Brown RA, Barros TP, Kumita JR, Yerbury JJ, Satapathy S, McDade K, Smith C, Luheshi LM, Dobson CM, Wilson MR (2017) Clusterin protects neurons against intracellular proteotoxicity. Acta Neuropathol Commun 5:81.

Guan PP, Yang LQ, Xu GB, Wang P (2021) Indomethacin disrupts the formation of beta-amyloid plaques via an alpha2-macroglobulin-activating lrp1-dependent mechanism. Int J Mol Sci 22:8185

Guerin DJ, Kha CX, Tseng KA (2021) From cell death to regeneration: rebuilding after injury. Front Cell Dev Biol 9:655048.

Gupta AK, Pokhriyal R, Khan MI, Kumar DR, Gupta R, Chadda RK, Ramachandran R, Goyal V, Tripathi M, Hariprasad G (2019) Cerebrospinal fluid proteomics for identification of alpha2-macroglobulin as a potential biomarker to monitor pharmacological therapeutic efficacy in dopamine dictated disease states of Parkinson's disease and schizophrenia. Neuropsychiatr Dis Treat 15:2853-2867.

Hastings GA, Coleman TA, Haudenschild CC, Stefansson S, Smith EP, Barthlow R, Cherry S, Sandkvist M, Lawrence DA (1997) Neuroserpin, a brain-associated inhibitor of tissue plasminogen activator is localized primarily in neurons. Implications for the regulation of motor learning and neuronal survival. J Biol Chem 272:33062-33067.

Hidalgo San Jose L, Sunshine MJ, Dillingham CH, Chua BA, Kruta M, Hong Y, Hatters DM, Signer RAJ (2020) Modest declines in proteome quality impair hematopoietic stem cell self-renewal. Cell Rep 30:69-80.e6.

Ikeda R, Kurokawa MS, Chiba S, Yoshikawa H, Ide M, Tadokoro M, Nito S, Nakatsuji N, Kondoh Y, Nagata K, Hashimoto T, Suzuki N (2005) Transplantation of neural cells derived from retinoic acid-treated cynomolgus monkey embryonic stem cells successfully improved motor function of hemiplegic mice with experimental brain injury. Neurobiol Dis 20:38-48.

Jaldín-Fincati JR, Actis Dato V, Díaz NM, Sánchez MC, Barcelona PF, Chiabrando GA (2019) Activated α2-macroglobulin regulates lrp1 levels at the plasma membrane through the activation of a Rab10-dependent exocytic pathway in retinal Müller glial cells. Sci Rep 9:13234.

Jeong S, Ledee DR, Gordon GM, Itakura T, Patel N, Martin A, Fini ME (2012) Interaction of clusterin and matrix metalloproteinase-9 and its implication for epithelial homeostasis and inflammation. Am J Pathol 180:2028-2039.

Kehl D, Generali M, Mallone A, Heller M, Uldry AC, Cheng P, Gantenbein B, Hoerstrup SP, Weber B (2019) Proteomic analysis of human mesenchymal stromal cell secretomes: a systematic comparison of the angiogenic potential. NPJ Regen Med 4:8.

Kim KM, Chung KW, Jeong HO, Lee B, Kim DH, Park JW, Kim SM, Yu BP, Chung HY (2017) MMP2-A2M interaction increases ECM accumulation in aged rat kidney and its modulation by calorie restriction. Oncotarget 9:5588-5599.

LaMarre J, Hayes MA, Wollenberg GK, Hussaini I, Hall SW, Gonias SL (1991) An alpha 2-macroglobulin receptor-dependent mechanism for the plasma clearance of transforming growth factor-beta 1 in mice. J Clin Invest 87:39-44.

Liu H, Reiter S, Zhou X, Chen H, Ou Y, Lenahan C, He Y (2021) Insight into the mechanisms and the challenges on stem cell-based therapies for cerebral ischemic stroke. Front Cell Neurosci 15:637210.

Liu Y, Chen YG (2020) Intestinal epithelial plasticity and regeneration via cell dedifferentiation. Cell Regen 9:14.

Ma JF, Liu LH, Zhang Y, Wang Y, Deng YL, Huang Y, Wang G, Xu W, Cui PJ, Fei QZ, Ding JQ, Tang HD, Chen SD (2011) Association study of clusterin polymorphism rs11136000 with late onset Alzheimer's disease in Chinese Han population. Am J Alzheimers Dis Other Demen 26:627-630.

Maetzler W, Tian Y, Baur SM, Gauger T, Odoj B, Schmid B, Schulte C, Deuschle C, Heck S, Apel A, Melms A, Gasser T, Berg D (2012) Serum and cerebrospinal fluid levels of transthyretin in Lewy body disorders with and without dementia. PLoS One 7:e48042.

Marino-Puertas L, Del Amo-Maestro L, Taules M, Gomis-Ruth FX, Goulas T (2019) Recombinant production of human alpha2-macroglobulin variants and interaction studies with recombinant G-related alpha2-macroglobulin binding protein and latent transforming growth factor-beta2. Sci Rep 9:9186.

Matsuda A, Itoh Y, Koshikawa N, Akizawa T, Yana I, Seiki M (2003) Clusterin, an abundant serum factor, is a possible negative regulator of MT6-MMP/MMP-25 produced by neutrophils. J Biol Chem 278:36350-36357.

McGinley LM, Sims E, Lunn JS, Kashlan ON, Chen KS, Bruno ES, Pacut CM, Hazel T, Johe K, Sakowski SA, Feldman EL (2016) Human cortical neural stem cells expressing insulin-like growth factor-i: a novel cellular therapy for Alzheimer's disease. Stem Cells Transl Med 5:379-391.

Musiał K, Augustynowicz M, Miśkiewicz-Migoń I, Kałwak K, Ussowicz M, Zwolińska D (2020) Clusterin as a new marker of kidney injury in children undergoing allogeneic hematopoietic stem cell transplantation—A pilot study. J Clin Med 9:2599.

Nielsen HM, Minthon L, Londos E, Blennow K, Miranda E, Perez J, Crowther DC, Lomas DA, Janciauskiene SM (2007) Plasma and CSF serpins in Alzheimer disease and dementia with Lewy bodies. Neurology 69:1569-1579.

Nilselid AM, Davidsson P, Nagga K, Andreasen N, Fredman P, Blennow K (2006) Clusterin in cerebrospinal fluid: analysis of carbohydrates and quantification of native and glycosylated forms. Neurochem Int 48:718-728.

Nonaka M, Yoshikawa M, Nishimura F, Yokota H, Kimura H, Hirabayashi H, Nakase H, Ishizaka S, Wanaka A, Sakaki T (2004) Intraventricular transplantation of embryonic stem cell-derived neural stem cells in intracerebral hemorrhage rats. Neurol Res 26:265-272.

Noormohammadi A, Calculli G, Gutierrez-Garcia R, Khodakarami A, Koyuncu S, Vilchez D (2018) Mechanisms of protein homeostasis (proteostasis) maintain stem cell identity in mammalian pluripotent stem cells. Cell Mol Life Sci 75:275-290.

Okada N, Kawakita T, Mishima K, Saito I, Miyashita H, Yoshida S, Shimmura S, Tsubota K (2011) Clusterin promotes corneal epithelial cell growth through upregulation of hepatocyte growth factor by mesenchymal cells in vitro. Invest Ophthalmol Vis Sci 52:2905-2910.

Pallardo-Fernández I, Iglesias V, Rodríguez-Rivera C, González-Martín C, Alguacil LF (2020) Salivary clusterin as a biomarker of tobacco consumption in nicotine addicts undergoing smoking cessation therapy. J Smok Cessat 15:171-174.

Polihronis M, Paizis K, Carter G, Sedal L, Murphy B (1993) Elevation of human cerebrospinal fluid clusterin concentration is associated with acute neuropathology. J Neurol Sci 115:230-233.

Prikrylova Vranova H, Henykova E, Mares J, Kaiserova M, Mensikova K, Vastik M, Hlustik P, Zapletalova J, Strnad M, Stejskal D, Kanovsky P (2016) Clusterin CSF levels in differential diagnosis of neurodegenerative disorders. J Neurol Sci 361:117-121.

Pucci S, Greggi C, Polidoro C, Piro MC, Celi M, Feola M, Gasbarra E, Iundusi R, Mastrangeli F, Novelli G, Orlandi A, Tarantino U (2019) Clusterin silencing restores myoblasts viability and down modulates the inflammatory process in osteoporotic disease. J Transl Med 17:118.

Qian C, Zhou FQ (2020) Updates and challenges of axon regeneration in the mammalian central nervous system. J Mol Cell Biol 12:798-806.

Saleh H, Afify A, Ahmed W, Daruish M (2020) Seminal plasma clusterin as a biomarker for spermatogenesis in varicocele patients before and after varicocelectomy. QJM 113:hcaa046.015.

Santos SD, Lambertsen KL, Clausen BH, Akinc A, Alvarez R, Finsen B, Saraiva MJ (2010) CSF transthyretin neuroprotection in a mouse model of brain ischemia. J Neurochem 115:1434-1444.

Satapathy S, Wilson MR (2022) Identifying new molecular players in extracellular proteostasis. Biochem Soc Trans 50:321-334.

Serifova X, Ugarte-Berzal E, Opdenakker G, Vandooren J (2020) Homotrimeric MMP-9 is an active hitchhiker on alpha-2-macroglobulin partially escaping protease inhibition and internalization through LRP-1. Cell Mol Life Sci 77:3013-3026.

Suzuki Y, Hashimoto K, Hoshi K, Ito H, Kariya Y, Miyazaki K, Sato M, Kawasaki Y, Yoshida M, Honda T, Hashimoto Y, Hosoya M (2019) Ratio of alpha 2-macroglobulin levels in cerebrospinal fluid and serum: an expression of neuroinflammation in acute disseminated encephalomyelitis. Pediatr Neurol 98:61-67.

Tarquini C, Pucci S, Scioli MG, Doldo E, Agostinelli S, D'Amico F, Bielli A, Ferlosio A, Caredda E, Tarantino U, Orlandi A (2020) Clusterin exerts a cytoprotective and antioxidant effect in human osteoarthritic cartilage. Aging (Albany NY) 12:10129-10146.

Thambisetty M, Simmons A, Velayudhan L, Hye A, Campbell J, Zhang Y, Wahlund LO, Westman E, Kinsey A, Güntert A, Proitsi P, Powell J, Causevic M, Killick R, Lunnon K, Lynham S, Broadstock M, Choudhry F, Howlett DR, Williams RJ, et al. (2010) Association of plasma clusterin concentration with severity, pathology, and progression in Alzheimer disease. Arch Gen Psychiatry 67:739-748.

Tsirka SE, Gualandris A, Amaral DG, Strickland S (1995) Excitotoxin-induced neuronal degeneration and seizure are mediated by tissue plasminogen activator. Nature 377:340-344.

Vancamp P, Gothie JD, Luongo C, Sebillot A, Le Blay K, Butruille L, Pagnin M, Richardson SJ, Demeneix BA, Remaud S (2019) Gender-specific effects of transthyretin on neural stem cell fate in the subventricular zone of the adult mouse. Sci Rep 9:19689.

Varma VR, Varma S, An Y, Hohman TJ, Seddighi S, Casanova R, Beri A, Dammer EB, Seyfried NT, Pletnikova O, Moghekar A, Wilson MR, Lah JJ, O'Brien RJ, Levey AI, Troncoso JC, Albert MS, Thambisetty M (2017) Alpha-2 macroglobulin in Alzheimer's disease: a marker of neuronal injury through the RCAN1 pathway. Mol Psychiatry 22:13-23.

West J, Satapathy S, Whiten DR, Kelly M, Geraghty NJ, Proctor EJ, Sormanni P, Vendruscolo M, Buxbaum JN, Ranson M, Wilson MR (2021) Neuroserpin and transthyretin are extracellular chaperones that preferentially inhibit amyloid formation. Sci Adv 7:eabf7606.

Wicher G, Fex-Svenningsen A, Velsecchi I, Charnay Y, Aldskogius H (2008) Extracellular clusterin promotes neuronal network complexity in vitro. Neuroreport 19:1487-1491.

Wilson L, Gale E, Chambers D, Maden M (2004) Retinoic acid and the control of dorsoventral patterning in the avian spinal cord. Dev Biol 269:433-446.

Wolf BB, Gonias SL (1994) Neurotrophin binding to human alpha 2-macroglobulin under apparent equilibrium conditions. Biochemistry 33:11270-11277.

Wright MC, Mi R, Connor E, Reed N, Vyas A, Alspalter M, Coppola G, Geschwind DH, Brushart TM, Hoke A (2014) Novel roles for osteopontin and clusterin in peripheral motor and sensory axon regeneration. J Neurosci 34:1689-1700.

Wyatt AR, Yerbury JJ, Berghofer P, Greguric I, Katsifis A, Dobson CM, Wilson MR (2011) Clusterin facilitates in vivo clearance of extracellular misfolded proteins. Cell Mol Life Sci 68:3919-3931.

Wyatt AR, Yerbury JJ, Ecroyd H, Wilson MR (2013) Extracellular chaperones and proteostasis. Annu Rev Biochem 82:295-322.

Yan P, Ren J, Zhang W, Qu J, Liu GH (2020) Protein quality control of cell stemness. Cell Regen 9:22.

Yepes M, Sandkvist M, Wong MK, Coleman TA, Smith E, Cohan SL, Lawrence DA (2000) Neuroserpin reduces cerebral infarct volume and protects neurons from ischemia-induced apoptosis. Blood 96:569-576.

Yerbury JJ, Poon S, Meehan S, Thompson B, Kumita JR, Dobson CM, Wilson MR (2007) The extracellular chaperone clusterin influences amyloid formation and toxicity by interacting with prefibrillar structures. FASEB J 21:2312-2322.

Zhao X, Henderson HJ, Wang T, Liu B, Li Y (2021) Deletion of clusterin protects cochlear hair cells against hair cell aging and ototoxicity. Neural Plast 2021:9979157.

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