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Review

Clusterin: Always protecting. Synthesis, function and potential issues

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ABSTRACT

In the last years, clusterin, a challenging and paradoxical apolipoprotein, has been of growing interest amongst a rising number of scientists. This enigmatic protein is present in all fluids of the organism besides within the intracellular matrix, and it plays diverse, and at times contrary, roles in a growing number of pathologies. It seems to vary its location and function to assure cellular survival being cytoprotective hence its significance in neuroprotection and cancer along with chemotherapy resistance. However, it can also lead to cellular arrest and its modulation to apoptosis. Additionally, it has been described to modulate pain, as well as linked to inflammation, cardioprotection, satiety and hunger, and possibly to addictive behaviour development. Thus, it has been postulated to be used both as a biomarker and a very explorable new therapeutic target for several conditions.

1. Introduction

Clusterin, apolipoprotein J (ApoJ), SPG2, TRPM-2 or CLU was first discovered and isolated in 1979 in rat testis [1]. It was named clusterin after the ability it demonstrated in aggregating blood cells *in vitro* [2]. At the time it was never believed to play so many important roles and certainly not imagined to be such a challenge for scientists. It is a ubiquitous multifunctional glycoprotein that is present in almost all fluids of the organism, as well as in the intracellular matrix in several locations. It carries out numerous functions even at times being dichotomic leading to outcomes that are opposite, what makes this protein even more enigmatic.

From the initial protein precursor, different isoforms can generate: a small nuclear isoform (~49 kDa)a medium size that remains in the cytosol and mitochondria (~53 kDa) or larger proteins glycosylated and cleavaged in the endoplasmic reticulum/Golgi apparatus that may be secreted in the form of α-βheterodimer outer the cell (~75–80 kDa). All of them differing in their functions [3].

Clusterin was first associated with Alzheimer's disease because of the chaperone activity that the secreted isoform presents. It is an important player in clearing misfolded proteins –such as β-amiloid amongst others, and cellular debris in the interstitial compartment surrounding tissue cells. Therefore, it has traditionally been given a neuroprotective role [4–6]. Moreover, it was reported that intermediate maturation isoforms of clusterin take part in gene translocation processes ensuring cell survival. Yet it is precisely in connection with this cellular protective role that it was further associated with cancer proliferation. Ironically, clusterin's protective effect here is meant to favor cellular survival. Following this line, in the past years clusterin has also been suggested to have a protective role against the oncologic pain derived from cancer treatment; furthermore it has also been proposed as a potential candidate to treat other types of pain including neuropathic and inflammatory [7–9]. In fact, recent studies advocate for an adjuvant role of clusterin in inflammatory conditions such as obesity, in which it has also been related to feeding control [10]. Just precisely, a connection betweenaddictive processes andthe levels of this protein have been suggested to happen [11,12]. Additionally, in the past years several works have also claimed out for a protective role in cardiac disease [13].

Clusterin is therefore ubiquitously expressed in most tissues of the human body, counting with a large presence in the central nervous system and endocrine tissues, among others. However, although separate studies claim on its importance for cellular survival, pain, hunger or cardiac protection, there is still a lack of an integrative view. Given the eclectic role of pathophysiology, the present work aims to offer an updated overview on the potential use of clusterin as a prognostic biomarker and candidate therapeutic target relying on such discipline, compiling information from its biological synthesis to latest publications on their physiological and protective roles.

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2. Clusterin synthesis

In humans, clusterin is coded by a 16Kb gene localized in chromosome 8p21-p12, that presents 11 exons (two of which are untranslated) of different sizes. The transcription of the CLU gene renders at least three mRNA isoforms in humans [14], and therefore several protein synthetic pathways (Fig. 1).

The canonical protein synthesis starts with the synthesis of the mRNA from the start codon located in exon 2 from resulting in a pre-protein of 449 aminoacids, from which the first 22 code for a signal of translocation to the endoplasmic reticulum [5]. Once the pre-protein is translocated, such sequence is removed and an N-glycosylation of six Asn residues takes place together with the formation of four or five disulfide bond formation, rendering the presecreted isoform of the protein (psCLU). This rich in mannose protein is translocated to the Golgi Apparatus where it is further glycosylated with complex carbohydrates increasing its maturation reaching a protein of around 70−80KDa.This highly glycosilated protein is cleaved by a furine-type protein between residues 227 and 228 rendering two subunits, an α N-terminal, and a β C-terminal, that afterwards are bonded by disulfide bonds rendering a completely mature protein, or secreted isoform (sCLU), an heterodimer of 2 subunits α and β of 35−40KDa [3,5,15–17] (Fig. 2).

Otherwise, an alternative splicing starting from the same gene takes place in between exon 1 and 3 erasing exon 2. This process renders a truncated protein lacking the translocation sequence thus it isn't transported to the endoplasmic reticulum [5,16,18]. From this translation emerges to the cytoplasm the non-functional or latent prenuclear isoform (pnCLU) of approximately 49KDa. Under certain cellular stress situations this immature isoform is transformed into a mature form or nuclear clusterin (nCLU) of 55 kDa that translocates to the nucleus where through its binding to Ku-70 is able to promote apoptosis through a caspase 3 dependent pathway [19–23] what was confirmed by the increase in Tunel staining as well as interaction with Bcl-xl as observed by [24] (Fig. 2) or through NF-κB signaling [25–27].

3. Clusterins role inside the cell

Contrarily to the function that this nuclear isoform appears to have as a proapoptotic protein, the functions of the canonical pathway are far more complex. Product of an intermediate glycosylation a presecreted almost mature isoform (psCLU) of 53KDa appears. This isoform under certain stress situations likephysiologic stresses, such as increased secretory load, or pathological stresses, such as the presence of mutated proteins [28,29], pharmacological treatments including paclitaxel [30] or even early life exposure to undernutrition [31] can bind in the endoplasmic reticulum to the reticular chaperone GRP87 (Bip) for its stabilization and translocation to the mitochondria [3,30,32]. Once inside the mitochondria, psCLU is able to sequester activated Bax, modulating the homoligomerization of the protein [33] hence inhibiting the formation of Bax-Bak complex that would induce the apoptotic cascade through permeabilization of the outer mitochondrial membrane (MOMP) and the following release of cytochrome c [34], therefore behaving as an antiapoptotic protein (Fig. 1). Moreover, the mitochondrial isoform of 45KDa has been described to reside in the mitochondrial matrix where it is proposed to be facilitating mitochondrial respiration in the healthy brain by regulating mitochondrial ribosomes, mitochondrial protein synthesis, thus ATP synthesis, as well as with the regulation of tricarboxylic acid cycle steps and oxidative phosphorylation [14,35].

On the other hand, when psCLU is located in the cytoplasm, it is able to stabilize Ku70-Bax complex, therefore preventing the arrival of Bax to the mitochondria [36]. In this same location it would also be able to bind to the cytotoxic substances leading to their proteasomal degradation [37] contributing moreover to the anti-apoptotic profile of the isoform of the protein.

Moreover, and reinforcing the anti-apoptotic role of clusterin, Pereira and co-workers (2018) described how clusterin can activate PI3K-AKT pathway. This activation leads to a phosphorylation of GSK3 that inhibits the phosphorylation of Bax, which is necessary for its activation [38,39]. Nonetheless, by inactivating GSK3, other of its multiple actions are also inhibited such as dopamine (DA) release.

4. Secreted clusterin: clusterin outside the cell

Clusterin was the first molecule described to act as a chaperone outside the cell, it facilitates extracellular clearance of misfolded proteins [40] in a similar manner as heat shock proteins (Hsp) do inside the cell. Briefly, it binds through hydrophobic interactions to proteins that are on folding pathways [3], and probably through binding to scavenger receptors to macrophages, it is able to induce their internalization and further metabolization, in an inverse glycosylation dependent manner, possibly also binding to LRP (LDL receptor-related protein) family receptors [41].

On the other hand, the secreted and fully mature isoform (sCLU) has been related to a large number of conditions but molecularly, once internalized into another cell, it has been described to have a proapoptotic role since it would be able to inhibit cellular proliferation because it is able to stabilize the synthesis of p53, that activates genes able to stop cell cycle at G1 [36] (Fig. 2) or at G0-phase [26,42].

5. Clusterin and neuroprotection

Its main source in the brain is fromastrocytic synthesis that secretes the protein to the extracellular space [5], but it has been described to be released by neurons in response to several neurological insults [4]. Thus it has been described to be overexpressed in excitotoxicity situations [43], following cerebral ischemia [44], traumatic brain damage [45,46], cellular stress associated with genetic deficiencies [47], in pathological amyloid-βaccumulations [6], or in cortical neuronal subpopulations of schizophrenia patients [48].

Regarding its relationship with neurodegenerative pathologies, it has been described playing an important role in several neurological

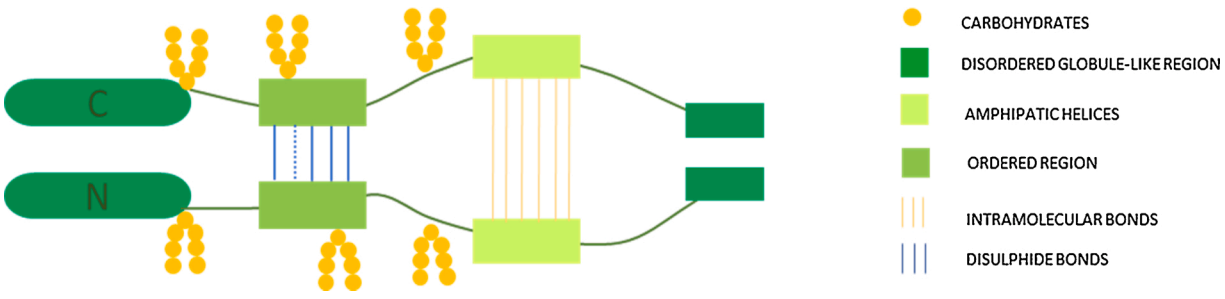

Fig. 1. Schematic illustration of clusterin. Illustration of the most mature and glycosylated isoform of the protein with 5 disulfide bonds binding the α and β subunits of the protein conforming the 80KDa secreted clusterin (sCLU).

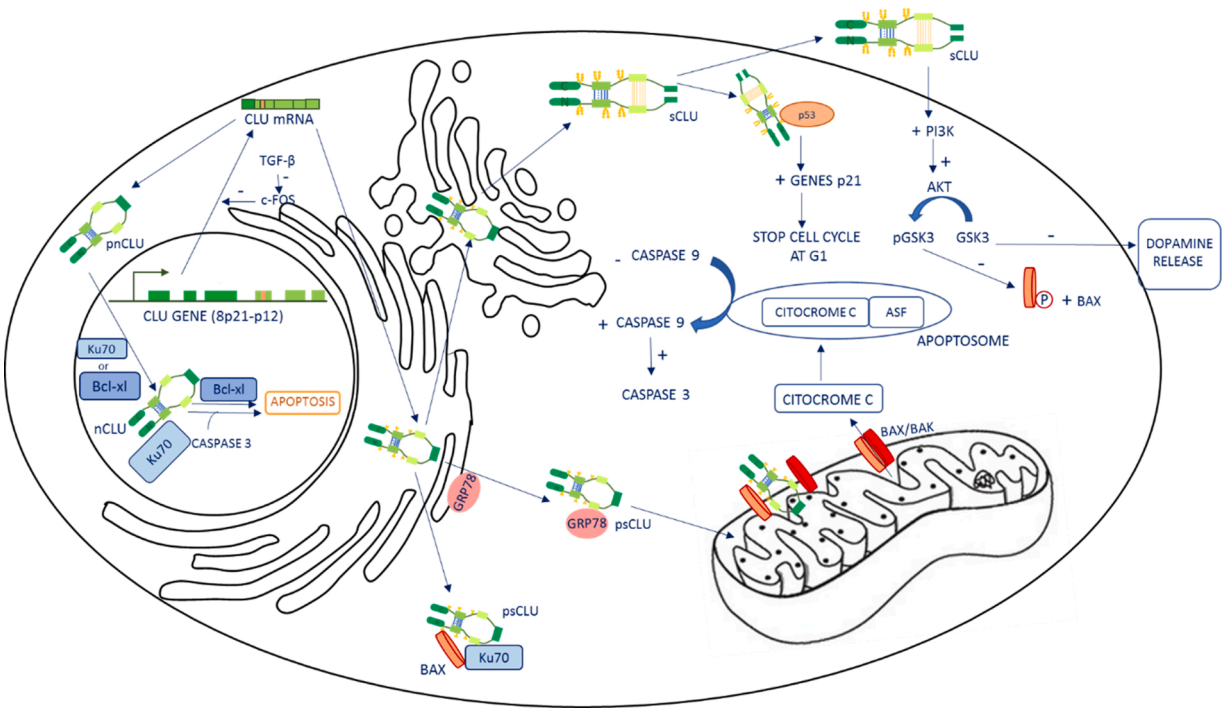

Fig. 2. Clusterin synthesis and functions inside the cell. AKTAk strain transforming (protein kinase B); ASF,absolute specificity factor (aspartate amino transferase); CLU, clusterin; nCLU, nuclear clusterin; pnCLU, pre-nuclear clusterin; psCLU, pre-secreted clusterin; sCLU, secreted clusterin; BAX, bcl-2-like protein 4; BAK, Bcl-2 homologous antagonist/killer; GRP78,glucose-regulated protein 78 KDa; GSK3, Glycogen synthase kinase 3;MRNA, messenger RNA; PI3K, phosphatidylinositol 3-kinase; p53, tumor protein p53KDa; TGF-β, transforming growth factor β.

diseases such as Alzheimer's disease, multiple sclerosis, Parkinson's disease amongst others.

Concerning Alzheimer's disease, severely affected brain regions in humans with developed Alzheimer's disease (AD) significant increases in both, secreted clusterin (sCLU) as well as total intracellular protein, have been described compared with controls [49,50]. In the same direction come the correlations that have been described between plasma levels of the protein and the lower volume of the entorhinal cortex, an area that atrophies in early phases of AD [51]. Moreover, clusterin concentration in cerebrospinal fluid of patients may be a clinically useful indicator of acute neuropathology. Elevated concentrations of clusterin were detected in patients following repeated convulsions, with spinal cord compression and demyelination [52]. In addition, clusterin concentration has been positively correlated with levels of neurogranin in cerebrospinal fluid in patients with different severities of cognitive impairment, indicating a direct link with synaptic degeneration [53]. Besides, and regarding synaptic degeneration, Jackson and co-workers described that the percentage of synapses containing clusterin is higher in APOE4 carriers, which is a genetic variant of predisposition of synaptic degeneration and its accumulation exacerbates synapse degeneration and synaptic accumulation of toxic oligomeric amyloid beta in human Alzheimer and mouse models of the disease [54]. Clusterin has also been described to increase concentrations of tau levels and its phosphorylation when injected into the rat hippocampus and in transgenic mouse models overexpressing tau, clusterin was also overexpressed [55], suggesting a direct tau protein interaction [50]. Other authors have described a correlation between clusterin plasma levels and changes in brain volume in mild cognitive impairment patients pointing towards the chaperone protective role of this isoform [56]. Thus, it has been thought to act by altering amyloid aggregation and through its chaperone function attempting amyloid-β clearance. This suggests a neuroprotective role [5] along with its attempt to clear its presence in the brain through its binding to LRP1 in the blood brain barrier [53,57].

In the same line, in the case of alpha-synucleinopathies, such as Parkinson's disease clusterin is co-localized with cortical Lewy bodies [58]. Interestingly, aggregates with a stronger clusterin concentration present a decrease in alpha-synuclein, probably due a role for clusterin in modifying its aggregation and clearing through its chaperone activity [5].

Regarding cognitive impairment, as a whole, three genetic polymorphisms of clusterin have been detected predisposing to such condition, rs11136000, rs2279590 and rs9331888 [59]. The variant allele of CLU rs11136000 seems to predispose to the development of late-onset of AD, such allele has also been detected in Parkinson's disease patients with cognitive impairment in drug naive stage and five years after where the memory and functional tasks were even more impaired than those of patients not expressing this allele [60].

Similarly, as several authors have described, hypoxia-ischemia in the brain also triggers CLU expression [5,61–64]. Likewise, in animal models of this pathology, both neuronal and astroglial cells express high levels of clusterin early after the ischemic damage, levels that are maintained, summed up to the evidence of a better recovery from middle cerebral artery occlusion in wild type mice that in animals lacking clusterin that presented a larger number of GFAP positive astrocytes and a poorer reconstruction of the ischemic area, supporting a protective effect of CLU against hypoxia-ischemia [65]. Moreover, human studies have demonstrated how an overexpression of CLU in humans decreased the presence of inflammatory cells and cell death, thus supporting the role as anti-apoptotic and crucial in cell survival and neuroplasticity after stroke [66].

6. Clusterin and undesired cellular survival

Supporting the anti-apoptotic role of sCLU, growing evidences have demonstrated that the over-expression of CLU in malignancies may contribute to tumor progression [67]. Additionally, several authors have suggested how sCLU might be involved in the development of resistances to radiotherapy treatments due to its anti-apoptotic function [68], and others such as Wang and colleagues support this hypothesis by

describing that sCLU could strengthen oxaliplatinum resistance through activating AKT/GSK3 pathway in hepatocarcinoma patients [67,69] where assumedly it would be able to inhibit the phosphorylation of Bak, necessary for its transport to the mitochondria and dimerization with Bax (Fig. 2). Moreover, metformin has been proved to have an anticancer role, it had been attributed to its inhibition of the AMPK signaling pathway but recently it has been shown to reduce clusterin expression, thus, inhibiting its antiapoptotic functions and therefore decreasing cancerous cell survival [70]. Furthermore, it has been directly related to metastasis development in several carcinogenic processes such as bladder, colon, hepatocellular carcinoma and renal cell carcinoma [70]. have reported that this relationship probably takes by inducing processes Epithelial-to-Mesenchymal Transition process by which epithelial cells lose their cell polarity and cell to cell adhesion, and gain migratory and invasive properties to become mesenchymal stem cells [71], hence it plays a role in modulating the phenotypes of cells, for cells with clusterin overexpression presented a spindle-shape morphology while cells with low clusterin levels were more cuboidal, what was reversed by silencing CLU expression, what also decreased metastatic and migratory processes in HCC cells [72]. On the other hand, TGF-β signaling may also play an important role in these processes since, in early stages, it suppresses tumor development and arrests cell proliferation and induces cellular death, but, in advanced stages of the pathology, it enhances clusterin expression, promoting invasion and metastasis, by inhibition of c-fos expression, that under physiological circumstances represses clusterin gene expression Fig. 2 [5,73–75].

7. Clusterin and inflammation

Several other studies have related clusterin with other inflammatory processes. Thus, it has been directly correlated with severity of asthmatic pathology in children [76]. On the other hand, an overexpression of clusterin has been reported in patients with osteoporosis colocalized with an overexpression of IL6 in the degenerating muscular tissues of these patients. This evidence suggests its involvement in the inflammatory myoblast degeneration that takes place in this pathology, and together with the findings that silencing CLU decreases the expression of CX3CR1 (a receptor highly expressed on Th1 activated T cells that by interacting with its ligand, induces chemotaxis of circulating monocytes and selective recruitment of Th1 lymphocytes responsible for chronic inflammatory processes [77,78], clusterin silencing has been postulated as a down modulator of the inflammatory response responsible for such muscular atrophy in osteoporotic conditions [79].

Moreover, proteomic studies have highlighted a differential expression of the protein and asignificative gene overexpression in obese patients [80–82]. A direct relationship has been suggested between this protein and adiposity, systemic inflammation and finally cardiovascular risk, hence Bradley et al., (2019) have reported a secretion by the adipocytes of this protein in response to high fat diet. This overexpressed clusterin is the communicator between adipocytes and liver through its binding to LPR2, thus inhibiting insulin signaling, promoting insulin resistance [83], gluconeogenesis and glucose absorption [84], consequently being an important player in the development of obesity, cardiovascular diseases, diabetes and might shed a light on the possible relationship between diabetes and AD [83]. Conversely, clusterin has been reported to improve endothelial dysfunction in diabetic patients by inhibiting mitochondrial fragmentation (Fig. 2) and probably by blocking the AMPK signaling [85], which on the other hand, is one of the proposed mechanisms through which apparently metformin, as has been previously described, inhibits cancer development, mechanism in which clusterin seems to be related.

8. Clusterin and cardioprotection

In addition, constitutively, together with apolipoprotein E (Apo E), it is part of J-HDL, that transports cholesterol from the tissues, amongst them adipose tissue, to liver for their removal. Consequently, both clusterin and J-HDL can alter cholesterol levels and the atherosclerotic risk [86,87]. Besides, the distribution of clusterin in the aortic wall increases with progression of atherosclerosis suggesting that clusterin forming the apoJ/paraoxanase-HDL particle may be protective against lipid peroxidation [88]. Contrarily, other authors have shown certain discrepancies for they found increased concentrations of the protein in the morbid obese patients but these didn't show an increased cardiovascular risk [89]. Besides, there is evidence regarding the expression of this protein along with heart failure being deposited in the human heart following myocardial infarction, colocalizing with complement factors C1q, C3d C4, and C9 on cardiomyocytes within the infarcted area, being synthesized by myocites apart from the possible internalization from circulating plasma clusterin [90]. Also, it has been highlighted clusterin is not strictly linked with cardiac pathologies. Its concentration seems to be proportional of that of PI3K which is known to be cardioprotective. It has been described to be increased in transgenic mice that overexpress PI3K and have healthy hearts, and depressed in those that have decreased levels of such protein and are susceptible to cardiac stress [13]. Therefore, it has been proposed as cardioprotective and a drug target of such pathologies, for as it is shown it Fig. 2, sCLU when interacting with other cells would be activating PI3K hence activating IGF1-PI3K pathway. Additionally [91,92], have revealed another cardioprotective role of clusterin since, following heart transplantation, it reduces the expression of several pro-inflammatory proteins such as TNF-α and BAX, through modulations of NF-κB signaling, what reduces cell death and ischemia reperfusion injury after transplantation, which is the main cause of heart damage.

9. Clusterin and addiction

Furthermore, clusterin has been related to food intake, being postulated as critical component in the regulatory feeding pathway. Thus, increased concentrations of the protein have been detected in hypothalamus of animals following fasting periods, increment that is corrected once animals are refed. Moreover, intracerebral administration of Apo-J produces anorexigenic effects, by inhibition of the orexigenic signals of NPY and AgRP, leading to a decrease in food intake and the subsequent weight loss. Results that are concordant to the findings of clusterin concentrations being increased in by satiety hormone leptin and decreased by hunger hormone ghrelin. On the other hand, silencing the expression the protein by using an antisensedesoxynucleotide results in hyperphagia, increase in body weight and adiposity [10]. Interestingly, authors have postulated the formation of leptin-clusterin complexes that would bind Lrp2 and Leprb for it to be endocyted shuttling the activation stat3 signaling with higher thus enhancing leptin signaling in the hypothalamus [93].

In parallel to the control it exerts upon satiety and hunger, it has been positively correlated with loss of control overeating in morbid obese patients [11] thus, it has been suggested as a biomarker for food addiction. Since food addiction has shown plenty of similarities with drug abuse and other addictions, the differential glycosylation of clusterin in alcohol dependent patients amongst other leptin binding proteins highlights its relevance in addictive processes [94]. Relationship also postulated by Freeman and co-workers [95] that saw a tendency to an increase of its gene expression in nucleus accumbens of chronic cocaine treated non-human primates. Likewise, clusterin concentrations seem to increase as smoking habbits do, since they increase with the duration and intensity of smoking and decrease after smoking cessation [12]. As clusterin has been previously linked to insulin resistance, we propose a potential mechanism through which it may be linked to addictive behavior and/or reward deficiency syndrome (Fig. 3), supported by the findings of [96] that describe how there was an increase in clusterin containing follicles in drug abusers that presented disorders in the hypothalamic dopaminergic system. This way, clusterin would bind to insulin receptor (INSR) and activate PI3K which would in turn

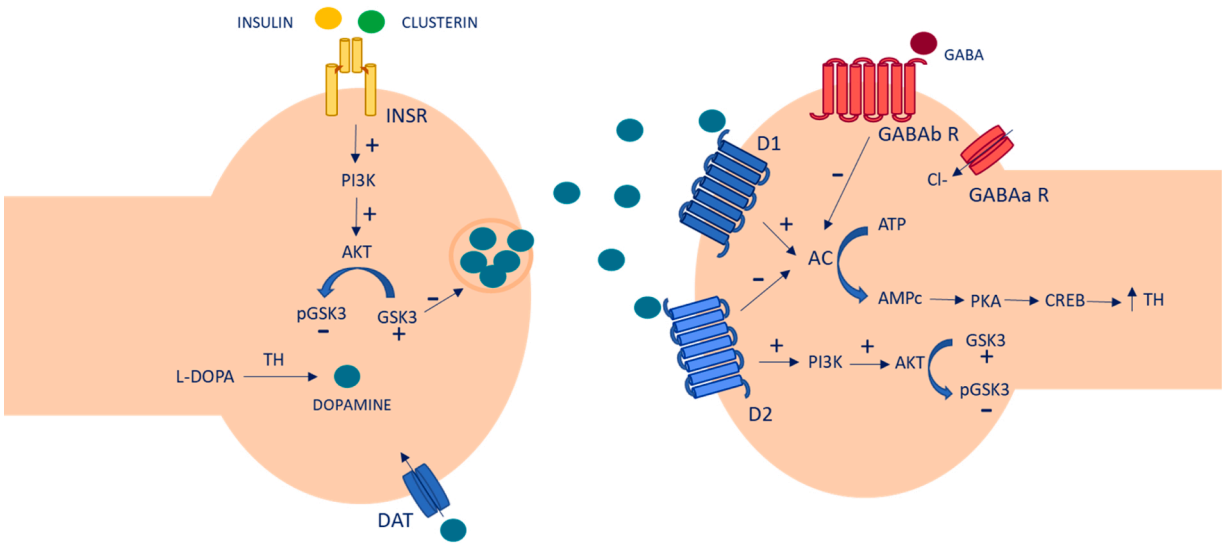

Fig. 3. Hypothesized mechanism of clusterin's relationship with dopamine disorder addictive behaviors. AC, adenylate cyclase; AKT, Ak strain transforming; AMPc, cyclic adenosine monophosphate; ATP, adenosine triphosphate; D1, dopamine receptor type 1;D2, dopamine receptor type 2; DAT, dopamine transporter; GABA, gamma-Aminobutyric acid; GSK3,; INSR, insulin receptor; PI3K, phosphatidylinositol 3-kinase; TH, Tyrosine hydroxylase.

activate AKT which would inactivate through a phosphorylation GSK3. Thus, activated GSK oversees promoting dopamine release into the synaptic cleft. Hence, the decrease of DA in the synaptic space would decrease the binding of DA to its receptor thus blocking its signaling.

A putative approach to implement this hypothesis in a translational manner would imply inhibiting the binding of clusterin to the receptor thus decreasing DA release. A possible approach to achieve such decrease may be the use of a competitive INRS receptor antagonist with a bigger affinity towards the receptor than that of clusterin but a lower one than that of insulin, thus achieving a blockade only by clusterin signalling but not by insulin and therefore not impeding normal insulinergic pathway. Moreover, the use of a molecule that could sequester clusterin in such location could be used to avoid its binding to the receptor, in the same way as clusterin does with Bax in the cytoplasm impeding Bax-bak oligomerization.

10. Clusterin and pain

Furthermore, and with a very relevant scope and importance, clusterin has been linked to pain. In this sense, several studies have related a decrease in clusterin concentrations in fluids of patients suffering from pain compared to that of healthy subjects. Thus [9], described how the proteomes of patients suffering from carpal tunnel syndrome showed a significant decrease in the levels of this protein compared to that of matched healthy controls, likewise, Zhu et al. (2011) described how the serum from patients with degenerative scoliosis analyzed by proteomics, showed significantly decreased levels of clusterin compared to controls [8]. Kropáčková and colleagues have also associated a lower clusterin serum concentration with higher pain scores (AUSCAN score index) and a visual analogue scale in patients with erosive hand osteoarthritis [97]. Moreover, Lind et al. in 2016 [98] have suggested a potential link between clusterin and a therapeutic response to peripheral neuropathic pain, where the relieve in pain, experienced by patients treated with spinal cord electromodulation, was accompanied by an increase in clusterin cerebrospinal fluid concentrations. Additionally, it has been described to be but strongly involved in the functional reorganization of the prefrontal cortex which has been recently reported in chronic pain conditions [99,100].

11. Translational clusterin: clusterin as a therapeutic target

Translating to the clinic the data obtained from basic research is the only path to make real advances and progresses tangible for people such as treating pathologies or preventing them. Although many speculations have been carried out concerning the applicability of these findings, have shortly been translated to clinic. It has been used as a biomarker for renal injury in clinical trials implying the use of inmunomodulators for renal pathologies [101], but the modulation of clusterin was not a key feature for such treatment, as it happened in the clinical trial Brott and coworkers carried out in search of renal biomarkers in patients with diabetes [102]. In the case of cognitive disorders, clusterin could be used as an informative multi-component preclinical marker [51,83] hence the atrophies early in AD it has been related to, or even as a biomarker of the linkage between diabetes mellitus and the so called "diabetes type 3": AD regarding it as a potential mediator in between both [83]. Regarding treatment of cardiac pathologies, it has never been used in patients [90], as no evidence have we found regarding clinical trials implying clusterin modulation and other pathologies but cancer.

In the field of cancer, it has been assayed in human clinical trials using OGX-011. OGX-011 is a 2′-methoxyethyl antisense oligonucleotide of clusterin. Both OGX-011 and the silencer that Gil and coworkers make use of are two antisense oligodesoxynucleotides-siRNA, that in accordance result in a decrease in clusterin synthesis, thus result in a decrease in cell proliferation and viability as well as in an increase in the sensitivity of cells to chemotherapeutic drugs [26] by inhibiting clusterins cytoprotective functions that lead to chemoresistance. This silencer was used by Beer and coworkers in combination with cabazitaxel and prednisone in prostate cancer phase III clinical trial not reporting any significant results [103]. Nonetheless, it was also employed in a Phase I study enrolling patients with prostate cancer where it resulted in a mean apoptotic index increase from 7.1% to 21.2% [104]. Phase II was carried out with patients with castration resistant prostate cancer (CRCP) where it was administered together with docetaxel. Chi and coworkers in this study described an increase of 7 months in the lifespan of patients receiving the combination of docetaxel-OGX-011. Phase III studies were started but results didn't seem very promising. Moreover, and speaking about other potential therapeutic targets, these patients showed a decrease in the pain they suffered of more than 50 % than those receiving docetaxel-alone, although no clinical trials have been carried out regarding such field on itself [105–107].

Likewise, Laskin and co-workers have reported how the use of this same OGX-011 (also named custirsen) in combination with Gemcitabine in a phase I/II clinical trial concerning patients with non-small cell lung cancer, significantly reduced plasma levels of clusterin while not producing any side effects other than those produced by chemotherapy. This decrease was accompanied by an increase in survival of 27 months compared to 16 months for patients who did not benefit from this combination treatment [108].

Considering the results obtained from these clinical trials it would be argued that more clinical studies should be addressed, but there is controversy about such matter. Zhang and collaborators discuss the lack of significant results in their meta-analysis [39], however, Peng and co-workers seem positive stating that Custirsen might have had a survival benefit in patients who had poor prognostic features, which deserves further study promoting a combination of the chemotherapy drug and a drug which inhibits clusterin expression [70]. Furthermore, several approaches seem obvious to carry out. For instance, the use of the previously mentioned use of deoxynucleotides by Gil and colleagues to control clusterin levels and functions in control overeating hence in the treatment of obesity and food addiction [10], or those approaches reviewed in Table 1, though none have yet been addressed.

In any case, and given clusterin is altered in many settings, its use as a biomarker seems very promising, but it would be impossible for it to suit as a unique diagnostic tool, thus, it should be complemented with clinical diagnosis, or even with the determination of other specific biomarkers for the suspected pathology. When targeted as a therapeutic tool, its management should be closely looked upon, or directly droven to cancerous cells by the use of nanomaterials, hence, if silenced inappropriately, it might lead to other disorders such as pain development or cardiac toxicity.

12. Future perspectives

In summary, clusterin seems to be a protective protein able to change its isoform and localization to assure cellular survival [5]. Hence, its modulation seems to be a tremendously encouraging approach to treat, cure or prevent numerous pathologies. Potentially it could be firstly used as a biomarker for addictive disorders [11] or neurodegenerative diseases. Clusterin expression, although in a directed or controlled manner, could be silenced to assure oncological treatment success [98,99], treat inflammatory conditions such as obesity, muscular atrophy in processes such as ostheroporosis. Moreover, its supplementation could be a target

Table 1
Potential Therapeutic targeting of Clusterin.

Physiological function	Pathology	Evidence	Potential therapeutic approach
neuroprotection	ischemic brain damage-stroke	Lack of CLU → poorer reconstruction of ischemic area (Imhof et al., 2006) Overexpression of CLU→ presence of inflammatory cells and cell death→cell survival and neuroplasticity after stroke (Wehrli et al., 2001).	enhance
	Alzheimer's Disease	Alteration of amyloid-β aggregation (Foster et al., 2019) Chaperone function→ amyloid-β clearance (Foster et al., 2019) In blood brain barrier clearance from brain (Nelson et al., 2017; J. Wang et al., 2020).	
	α-synucleinopathies	Alteration of α-synuclein aggregation (Foster et al., 2019) Chaperone function→α-synuclein clearance (Foster et al., 2019	
anti-inflammatory agent	osteoporosis	CLU silencing→ inflammatory response→in muscular atrophy (Pucci et al., 2019)	silence
	asthma	+ correlation with severity of asthmatic pathology in children (Sobeih et al., 2019)	enhance (anti-inflammatory properties?)
	heart transplantation	pro-inflammatory proteins (TNF-α, BAX)→ cell death and ischaemia reperfusion injury after transplantation→ heart damage (Liu et al., 2018)	enhance
cardioprotective	cardioprotection	+ PI3K activating IGF1-PI3K pathway → cardioprotective (Bass-Stringer et al., 2020)	enhance
	atherosclerosis and cholesterol clearance	CLU is part of J-HDL→ transports cholesterol from the tissues to liver for removal (Gelissen et al., 1998; Hoofnagle et al., 2010) CLU forming the ApoJ/paraoxanase-HDL particle → protective against lipid peroxidation (Ishikawa et al., 2001)	
food intake regulator	obesity	Intracerebral administration of ApoJ→ anorexigenic effects→ – of orexigenic signals of NPY and AgRP→ in food intake→weight loss(Gil et al., 2013) Suggested as a biomarker for food addiction (Rodríguez-Rivera et al., 2019)	enhance
reward pathway modulator	addictions	Differential glycosylation in alcohol dependant patients (Kratz et al., 2014) Gene expression in *nucleus accumbens* of chronic cocaine treated non-human primates (Freeman et al., 2001)	block
pain modulator	pain	pain relieve→ in CLU (that was underexpresed) (Lind et al., 2016)	enhance
anti-apoptotic	chemotherapy	CLU anti-apoptotic function → development of resistances to radiotherapy (Zellweger et al., 2002) CLU + AKT/GSK3 pathway→oxaliplatinum resistance (Zheng et al., 2020)	inhibit
	prognostic	Over-expression of CLU in malignancies→ tumour progression (Wang et al., 2020)	diagnosis
	metastasis	Related to metastasis development in bladder, colon, hepatocellular carcinoma and renal cell carcinoma (Peng et al., 2019) CLU induces EMT processes→cells gain migratory and invasive properties (Peng et al., 2019)	inhibit
apoptotic	cancer	nCLU→nCLU binds Ku-70→promote apoptosis through a caspase 3 dependent pathway (Leskov et al., 2003; Caccamo et al., 2005)	enhance
transporter	drug delivery	Deglycosylation of CLU →the cellular uptake of nanocarriers covered with these proteins (Ghazaryan et al., 2019)	use as drug delivery systems with decreased glycosylation

AgRP, agouti-related protein; AKT, Ak strain transforming; Apo-J, apolipoprotein J; BAX, bcl-2-like protein 4; CLU, clusterin; nCLU, nuclear clusterin; GSK3, Glycogen synthase kinase 3; EMT, epithelial-mesenchymal transition; IGF1, insulin-like growth factor-1; J-HDL, high density lipoprotein J; NPY, neuropeptide Y; PI3K, phosphatidylinositol 3-kinase; TNF-α, tumor necrosis factor α.

to ameliorate neuropathic pain [7], or as a neuroprotector for ischemic brain injury, Alzheimers disease or α-synucleinopathies [5]. Furthermore, its enhancement could be used as cardioprotector in atherosclerotic events and as a cholesterol clearance agent [86–88], as well as an antiinflamatory adyuvator for heart transplantation [91,92]. Besides, it could be used as a transporter to enrich drug delivery. Undoubtedly, its study seems to be extremely promising in many fields to further understand this enigmatic protein and its applicability.

Author contributions

CRR: design of the study and writing of the manuscript. MMG: contributed to the writing and preparation of the manuscript. MMA and CGM: preparation of the manuscript. CG: design, coordination, revision and final approval of the manuscript. All authors read and approved the final version.

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Declaration of Competing Interest

The authors report no declarations of interest.

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