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From *corpora amylacea* to wasteosomes: History and perspectives

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ABSTRACT

Corpora amylacea (CA) have been described in several human organs and have been associated with ageing and several pathological conditions. Although they were first discovered two centuries ago, their function and significance have not yet been identified. Here, we provide a chronological summary of the findings on CA in various organs and identify their similarities. After collecting and integrating these findings, we propose to consider CA as waste containers created by specific cells, which sequester waste products and foreign products, and assemble them within a glycan structure. The containers are then secreted into the external medium or interstitial spaces, in this latter case subsequently being phagocytosed by macrophages. This proposal explains, among others, why CA are so varied in content, why only some of them contain fibrillary amyloid proteins, why all of them contain glycan structures, why some of them contain neo-epitopes and are phagocytosed, and why they can be intracellular or extracellular structures. Lastly, in order to avoid the ambiguity of the term amyloid (which can indicate starch-like structures but also insoluble fibrillary proteins), we propose renaming CA as "wasteosomes", emphasising the waste products they entrap rather than their misleading amyloid properties.

1. Introduction

The presence of ageing-related granular structures has long been known in several human tissues, and was first described in histopathology reports. *"That is to say, in the prostate gland, which was enlarged, and, in its external circumference, of a red color inclining to brown, I found within the remaining part of its substance; which was in other respects in a natural state; granules of tobacco as it were, of a yellowish colour inclining to blackness; and those in several places. (…) But of what nature are these granules? For I have found them in many bodies, and not then for the first time"*. This description was given by Morgagni in 1779 (Morgagni, 1779), and seems to be the first recorded observation indicating the presence of granules in the prostate gland (Prather and Skinner, 1956).

Similar granular bodies were also described by Purkinje in 1837, in the brain of elderly patients (Catola and Achúcarro, 1906), while Virchow found them in brain, spinal cord, at the neck of the bladder and in the so-called female prostate (Eastman, 1897). In 1854, Virchow noted that the granules shared some similarities with starch, and called them *corpora amylacea* (CA), i.e., starch bodies in Latin (Virchow, 1854). Since then, these bodies have commonly been referred to as CA. Friedreich described them in the respiratory organs (Friedreich, 1856), Hildebrand in a sarcoma of the sternum, in 1895, and Lubarsch in a tumour of the suprarenal capsule (Eastman, 1897).

In 1897, Eastman wrote *"Widely varying hypotheses concerning the histogenesis of these bodies have been proposed by those whose attention they have attracted, the same after painstaking investigations, but none has led to an agreement as to the meaning of the observations made"*. Today, more than two centuries later, his words remain true, as the meaning of these granular structures has not yet been clarified.

To date, the CA in each organ or tissue have been analysed or interpreted almost exclusively in terms of the organ or tissue in which they occur, without taking into account what is known about CA in other organs or structures and thus without adopting a broader perspective. In this review, we provide an extensive review of the findings on CA in the various human tissues and identify their similarities and differences in terms of composition, appearance and hypothesised function. As neither

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the function nor the pathophysiological significance of CA has yet been identified, two centuries after they were first described, our overview of CA will help to clarify these aspects.

Before starting, it should be noted that the term amyloid (i.e., starch-like in Latin) is currently used to describe two different kinds of structure: polyglucosan structures similar to starch, but also some types of fibrillary proteins that tend to aggregate, such as β-amyloid in Alzheimer's disease or synuclein in Parkinson's disease. Use of the term amyloid to describe these proteins reflects the original erroneous identification of these proteinaceous substances as starch because they stain with iodine, considered a marker of starch-like structures. In the literature, the concept of amyloid bodies frequently refers to proteinaceous amyloid bodies, whereas amylacea bodies or corpora amylacea usually refer to polyglucosan amyloid bodies. However, these terms are sometimes used interchangeably, generating confusion and misinterpretation. In order to differentiate between the two structures, it should be borne in mind that polyglucosan amyloid structures stain with Periodic acid-Schiff (PAS), whereas the proteinaceous structures stain with either Congo red or thioflavin. In order to avoid confusion, here we will use the terms amylacea(p) and amyloid(p) to refer to the proteinaceous structures, and amylacea(s) and amyloid(s) to refer to starch or carbohydrate structures. The term amyloidosis will be reserved for the abnormal build-up of amyloid(p) in tissues or organs.

2. Chronological review

2.1. Corpora amylacea in the central nervous system

Since CA were first described in the brain by Purkinje and Virchow, many studies have examined these structures in the central nervous system (CNS). Robertson (1900) argued that CA were the product of cell degeneration, while Ellis (1920) described them as being generally associated with normal ageing. In a book on nervous system pathology published in 1923, Buzzard and Greenfield ruled out the idea that these bodies had any pathological significance, and this opinion endured for many years (Buzzard and Greenfield, 1923). Ferraro and Damon (1931) published an article reviewing the findings to date on the origin of these bodies in several tissues and claimed that they were merely "post-mortem" artefacts formed by protein precipitates. In 1933, large numbers of CA stained by haematoxylin and eosin were described in the *filum terminale* from several cases irrespective of age, sex or cause of death (Harmeier, 1933). They were located beneath the pia mater but also formed masses scattered throughout the tissue, in which large numbers of glial cells, including astrocytes, were also found (Tarlov, 1938). However, no study reported the possible function or meaning of these bodies at the end of the spinal cord.

In 1953, Alder conducted a detailed study of CA in the CNS, and described them as amyloid(s) structures that were abundant in the subpial and subependymal regions (Alder, 1953). He observed that their presence constituted one of the typical changes that occurred in senile and senescent brains, although they were also encountered under a variety of conditions in widely varying amounts and at different sites in the CNS. Subsequent studies indicated that brain CA were located within the processes of astrocytes (Ramsey, 1965), but others found them in neurons (Anzil et al., 1974). Several attempts were made at the time to elucidate the composition of CA. Some studies demonstrated that brain CA were not amyloid(p) deposits because they did not stain with Congo red or possess the typical rigid fibrillary structure, but instead contained a glycogen-like substance to which phosphate and sulphate were bound (Ramsey, 1965; Stam and Roukema, 1973). In 1969, Sakai and co-workers developed the first method to isolate CA, and observed that samples from patients aged over 70 years old were strongly stained with both iodine and PAS-dimedone. They determined that CA were formed mainly by glucose polymers and did not contain fucose or mannose. No evidence was obtained of significant quantities of mucopolysaccharides, mucoproteins or glycoproteins, but small amounts of protein and phosphate were detected. The amount of hexoses was estimated at about 68.4% (by weight), that of proteins 8.1% and the remaining 23.5% was unidentified (Sakai et al., 1969a, 1969b). They concluded that CA were round bodies lying inside the cytoplasm of fibrillary astrocytes and the result of a defect in glycogen metabolism. They found CA in the hippocampus, subependymal zones of the ventricles and beneath the pia, and indicated that proximity to cerebrospinal fluid (CSF) was a prominent feature of their distribution.

In 1980, Avendano et al. examined one hundred autopsy eyes and found CA in 93% of cases, either in the optic nerve or the inner retinal layers, being more common in older individuals. CA were round or oval and measured 2–20 μm in diameter, with those in the retina being smaller than those in the optic nerve. CA were usually present as intracellular structures containing randomly oriented, elongated and straight 6–7 nm thick filaments, were PAS positive and were composed of sulphated polysaccharides. In some cases, CA were surrounded by myelin, which led the authors to suggest that these structures contained degenerated products of axons rather than of glial cells, although they did not rule out an association with the degeneration of glial cells. Kubota et al. (1993) also studied the presence of CA in sections of the retina and the optic nerve from patients with malignant melanoma of the choroid, patients with glaucoma and control patients. The count of CA in sections from non-glaucomatous subjects increased significantly with advancing age and CA were more abundant in eyes with melanoma than in eyes with glaucoma. The authors concluded that CA represent intraneuronal ageing products that are diminished in eyes with end-stage glaucoma due to neuronal loss.

Research interest in these bodies in the nervous system increased when they were described to accumulate in the human brain in the course of normal ageing (Mrak et al., 1997), and to a much larger extent in Alzheimer's disease (Cissé et al., 1993; Inoue et al., 1996) and other neurodegenerative conditions (Chung and Horoupian, 1996; Robitaille et al., 1980). In 1994, Singhrao and colleagues published an article about the origin of these bodies and proposed that they were accumulations of waste products from neurons and oligodendrocytes (Singhrao et al., 1994). In 1995, Schipper and Cissé determined that CA progressively accumulated in periventricular regions with advancing age, were astrocytic in origin and contained various heat shock proteins and ubiquitin(Schipper and Cissé, 1995). In biopsied material from the vestibular root entry zone in cases of Meniere's disease, Sbarbati et al. (1996) observed at ultrastructural level that CA were sited in astroglial processes and mainly located in the *glia limitans*, near the pial region. In some CA, the astrocytic cytoplasmic membrane presented folds that created fissures which, according to these authors, could split the CA apart, allowing them to escape into the pial connective tissue or subpial space. In these cases, CA could be observed without the cytoplasmic membrane, i.e., in an extracellular location. Moreover, Schipper and Cissé (1995) suggested that CA were derived from autofluorescent Gomori-positive astrocytic granules which reside in periventricular regions of the senescent CNS. They proposed that, in the ageing human brain, degenerating mitochondria within periventricular astrocytes gave rise to autofluorescent cytoplasmic granules and CA.

In order to provide an insight into the composition of CA, Steyaert et al. (1990) purified and analysed CA from elderly individuals without neurological disease. Most CA showed a spherical shape but some of them displayed an ovoid or even an elongated shape and they presented a wide range of sizes. In phase-contrast microscopy, isolated CA showed a dense core surrounded by a rim of lighter material, while by scanning electron microscopy (SEM), they appeared to possess a lumpy surface. The amount of protein in the isolated CA was about 3.6% of the total dry weight. With respect to identification of the proteins contained in CA, different studies have been performed, mainly based on immunohistochemical procedures. Loeffler et al. (1993) described the presence of tau protein in CA from human retina and optic nerve. Amyloid precursor protein (Tate-Ostroff et al., 1989) and proteins specifically involved in ageing or stress, such as heat shock proteins (Iwaki et al., 1996),

ubiquitin (Kawashima et al., 1999) and advanced glycation end products (Iwaki et al., 1996; Kimura et al., 1998), have also been identified in brain CA. Hoyaux et al. (2000) studied the presence of S100 proteins in brain CA, which are calcium-binding proteins that have been described as being involved in neurodegenerative diseases (Li et al., 1998; Mrak et al., 1996). They detected the presence of S100 A1, A2, A3, A4, A5, A6, A8, A9 and A12, but not S100B, which is abundant in astrocytes and to a lesser extent in neurons from normal brain. The authors suggested that S100B could be rapidly degraded by the normal cell machinery and did not accumulate in CA, which may host substances escaping normal cell catabolism. A1, A8 and A9 were the most frequent S100 proteins found in CA, with A8 and A9 being highly expressed in activated granulocytes and found in serum from patients with chronic inflammatory disorders (Kerkhoff et al., 1998).

Chung and Horoupian (1996) considered CA a marker for mesial temporal sclerosis, the most frequent abnormality in temporal lobectomies performed for medically intractable seizure disorders. In mild cases, moderate to abundant numbers of CA were present in extrahippocampal tissues, showing a predilection for the white matter parenchyma, but in the most severe cases, massive deposits of CA were seen in the pyramidal layer, endfolium and dentate fascia of hippocampus, in a distribution paralleling the neuronal loss that characterises mesial temporal sclerosis. These bodies were PAS positive and associated with some scattered reactive astrocytes (GFAP-positive), and thus an astrocytic role in the mechanisms underlying mesial temporal sclerosis was proposed.

Cavanagh (1998) supported the neuronal origin of brain CA, as he observed that the number of CA decreased in the spinal cord with the loss of neurons in motor neuron degeneration. Moreover, he hypothesised that CA may contribute to the removal of waste materials of highly metabolically active cells, as an analogy to the lysosome-lipofuscin system. In 1999, Cavanagh wrote an extensive review of CA and concluded that they may exert an important role in collecting products from cell metabolism, mainly during ageing but also in diseases in which many potentially toxic waste products are produced (Cavanagh, 1999). He suggested that age-related products of the glycation process of long-lived proteins become incorporated into a glucose polymer mass, which may grow in size over time and eventually be retained intracellularly, for example in cardiac myocytes and some axons, or transported by astrocytes to various brain surfaces. However, he also acknowledged that their exact function was not known yet.

Several studies continued to provide evidence that CA are a product of neurons. CA were observed in patients with pharmacoresistant epilepsy, especially in areas of neuronal loss (Nishio et al., 2001). In a 2008 article about CA in the brain of patients with multiple sclerosis, Selmaj et al. (2008) reported that these structures accumulated remnants of neurons that were degenerating. A year later, Meng and co-workers concluded in their study that CA were conglomerates of proteins from neurons that were degenerating and blood elements that had entered the brain when the blood-brain barrier had been broken (Meng et al., 2009).

However, in a study of neuromyelitis optica (NMO), Suzuki et al. (2012) strongly supported the hypothesis that CA were a signal of astrocyte rather than neuron destruction. In fact, some authors consider that NMO is an astrocytopathy provoked by an autoantibody against aquaporin-4 (Lennon et al., 2005; Roemer et al., 2007; Suzuki et al., 2012). Suzuki et al. (2012) reported that CA were expelled from astrocyte processes and phagocytised by macrophages in early phase lesions of NMO in the optic nerve, the spinal cord or the *medulla oblongata*. In the lesions, the phagocytised CA were significantly smaller than intact CA and both were PAS positive. A subsequent study of the same disease also found numerous phagocytosed CA within the infiltrating macrophages in the necrotic lesion (Ohara et al., 2019).

Following another line of research, the olfactory tract of patients with Alzheimer's disease and controls was analysed because olfaction declines with ageing and appears to be a prodromal sign of cognitive impairment in progressive neurodegenerative diseases (Bathini et al., 2019). This study revealed an abundance of CA in control subjects but a decline in their density in the first stages of the disease, which appeared to persist over the course of the disease. Moreover, a gradual shift was observed in cytoskeletal proteins with increasing severity of dementia. These bodies were round, with a diameter greater than 10 μm, and extracellular. They showed negative staining for myelin, thus ruling out any oligodendrocyte-derived content. After performing staining for Jagged 1, MAP2, GAD67, PDS95 and synaptophysin, the authors concluded that CA from the olfactory tract were of neuronal origin and contained synaptic markers, neurosignalling molecules and cytoskeletal proteins with an ensheathing glial layer.

Meanwhile, a recent study using label-free multiphoton microscopy found that CA are composed of polyglucosans with an unusual, abnormally branched amylopectin-like structure. Moreover, the study proved that CA are not located within axons (Galli et al., 2018). With respect to CA composition, several fungal and bacterial proteins have recently been described in brain CA, contributing to the complexity of the proteins that form part of these structures (Pisa et al., 2016, 2018). Mold et al. (2018) found mineralised deposits in CA from the hippocampus of a multiple sclerosis patient, and again, a role for CA in collecting the remnants of cell death was suggested. Den Haan et al. (2018) reported the presence of amyloid-β in CA from the retina of patients with Alzheimer's disease and controls, identified by Kluver-PAS staining. These CA were described as rounded extracellular deposits and were positive for 6E10 (amyloid-β1–16) and 12F4 (amyloid-β1–42) antibodies but negative for 4G8 (amyloid-β17–24) and an APP c-terminal antibody.

In 2017, our group described the presence of neo-epitopes in CA from the hippocampus of patients with Alzheimer's disease, and the existence of plasmatic IgM natural antibodies that recognise these neo-epitopes (Augé et al., 2017). It should be noted that neo-epitopes are epitopes associated with the elimination of residual products and are commonly recognised by natural antibodies of the IgM isotype. Given that plasmatic IgMs do not cross the blood-brain barrier, natural IgMs do not have access to CA unless the blood-brain barrier is injured or CA are extruded out of the brain. Our findings supported the idea that CA, with their neo-epitopes as targets for the immune system, are waste containers involved in protective or cleaning mechanisms. Moreover, we reported that some positive immunostaining results described in several reports analysing CA might have been induced by contaminant IgMs present in commercial antibodies, giving rise to false positive results and indicating the need to revise the immunohistochemistry studies performed on CA. In 2018, we ruled out the presence of tau protein and β-amyloid peptides in CA, at least at immunofluorescence detection levels, but detected the presence of ubiquitin and p62 proteins, both associated with waste substance elimination processes, and glycogen synthase, an indispensable enzyme for polyglucosan formation (Augé et al., 2018a). A recent study by Wander et al. (2020) described the presence of tau protein in some, but not all, CA from control subjects and Alzheimer's disease patients, and also found astrocytes associated with them. They reported a potential negative correlation between tau-positive CA and the severity of Braak staging, and suggested that CA could be a mean for astrocytes to clean neuronal debris, including those induced by age-related stress.

Based on correlative serial block-face scanning electron microscopy (SBF-SEM) and transmission electron microscopy (TEM), Navarro et al. (2018) concluded that brain hippocampal CA are primarily composed of densely packed, aggregated lipid membrane fragments and disrupted cellular organelles, such as mitochondria and lysosomes, together with glycogen granules and digestive vesicles. They suggested that CA originated from aggregated cell components that formed when intracellular biochemical properties were perturbed, and that the bulk of membranous and glycosylated cellular material was of lysosomal origin. In 2019, we showed that CA were intracellular astrocytic structures, as they were surrounded by a plasma membrane and included intermediate filaments compatible with GFAP (Augé et al., 2019). This was the first study to show the ultrastructure of immature CA, which present distinctive

characteristics with respect to mature CA. These latter contain an external region which accumulates residual products, such as degenerating mitochondria and membrane fragments, and an inner region with fibrillary material. Meanwhile, immature CA contain an inner region that is less structured and less compact than that of mature CA and also contain mitochondria, cellular debris and membranous blebs located inside and surrounding the inner structure. In the same study, we also showed that the neo-epitopes present in CA were uniformly localised throughout the entire structure.

Also in 2019, we demonstrated that CA are released from the brain to the CSF and are present in the deep cervical lymph nodes (DCLNs), into which the CSF drains through the meningeal lymphatic system (Riba et al., 2019). Moreover, we showed that CA can be phagocytosed by macrophages. Accordingly, we postulated that CA from human brain act as containers that collect waste products and participate in a mechanism to clean the brain. Moreover, we hypothesised that CA may contribute in some autoimmune brain diseases, exporting brain substances that interact with the immune system, and suggested that CA may contain biomarkers that could aid in the diagnosis of certain brain diseases.

2.2. Corpora amylacea in peripheral nerves

CA have also been found outside the CNS, in peripheral nerves (reviewed in Cenacchi et al., 2019). They have been described as a hallmark of chronic vestibular nerve impairment in patients with intractable Meniere's disease (Wang et al., 2019). The pathological changes reported in this study demonstrated that CA formation is highly correlated with the degree of central vestibular nerve impairment, and the authors suggested that CA assist in the clean-up of abnormal materials such as cell debris or lipofuscin. In these cases, no positive correlation was observed between CA density and ageing. From a broader perspective, it has been estimated that CA are present in sural peripheral nerves in up to 8.5% of the general population, almost always associated with polyneuropathies, and showing an increasing prevalence with age (Busard et al., 1990). However, as the sural nerve is a sensory nerve and CA seem more prone to accumulate in motor nerves (Cavanagh, 1999), the incidence of CA in nerves in the general population may be higher than 8.5%. Other studies have indicated the presence of CA in peripheral nerves, and most have described them as intraneuronal or intra-axonal deposits (Yagishita et al., 1977; Komure et al., 1985; Yoshikawa et al., 1990; Matsumuro et al., 1993; Lu et al., 2016). However, Wang et al. (2019) observed CA within the axonal area, but also found them in the endoneurium and epineurium.

2.3. Corpora amylacea in the prostate

Morgagni observed granular concretions in the prostate gland in 1779 and regarded them as a pathological product of precipitation in prostate secretion (Morgagni, 1779). Later, Paulitzki found two different types of concretions: those that contained starch, as they stained with iodine and were degraded by saliva (supposedly due to their amylase content), and those which did not (Eastman, 1897). Posner also studied prostatic concretions but did not observe any staining with iodine, and thus concluded that prostate concretions did not contain vegetable starch. He suggested instead that they contained lecithin, and classified these structures as calculus (Eastman, 1897). Seigert contended that these structures in the prostate resulted from the union of cell products, gland secretions and tissue fluids, and indicated that they frequently calcified. He attributed two principal qualities to these structures: a strong light-reflecting power and high resistance to the strongest chemical reagents (Eastman, 1897). After examining several prostates, Eastman (1897) reported that prostatic CA were related to degeneration of the epithelium, contained amyloid(s) material and exhibited broad concentric laminations. From that time, prostatic CA are usually considered as lamellated structures. In addition, Marx et al. (1965) indicated that prostate CA were related to epithelial cell desquamation and degeneration.

Smith (1966) observed that many studies concerning prostate CA, concretions and calculi had been published and that the data were confusing. According to Röcken et al. (1996), prostate could contain different types of endogenous and exogenous stones, the latter being formed in the bladder or the urinary system. Furthermore, endogenous stones could be divided into two entities: concretions, which consisted mainly of salt precipitates with apatite and whitlockite, had little protein content, were calcified, were mainly found in atrophic glands, did not stain with Congo red and were not deposits of amyloid(p) (Fox, 1963; Torres Ramirez et al., 1980; Sutor and Wooley, 1974); and prostatic CA, which have been described as a proteinaceous matrix which stained with Congo red, showed an X-ray diffraction pattern consistent with amyloid (p) and had a fibrillar ultrastructure (Schrodt and Murray, 1966; Gueft, 1972; Cross et al., 1992). All this evidence suggested that they were amyloid(p) deposits. Moreover, prostatic CA contain mucopolysaccharides, a characteristic of all amyloid(p) deposits (Pasqualucci and Macha, 1968).

An immunohistochemical study of the prostate in people aged over 85 years old revealed hyperplasia in every studied prostate, and CA were localised exclusively within the zones of hyperplasia (Röcken et al., 1996). The CA showed a polymorphic shape with an irregular inner structure and an eosinophilic appearance when stained with haematoxylin and eosin. Their size varied from as small as a single epithelial cell to as large as the entire lumen of a hyperplastic gland duct. These CA were homogeneously immunostained with anti-amyloid β2 microglobulin (Aβ2M) and intense immunostaining with anti-Aβ2M was also observed of the hyperplastic epithelium surrounding CA (Röcken et al., 1996). β2 microglobulin is known to be the precursor protein of amyloid deposits associated with long-term haemodialysis (Gejyo et al., 1985), which relates CA to amyloid(p) deposits. However, according to Cohen et al. (2000), the staining with anti-Aβ2M was merely a false staining produced by endogenous biotin reactivity.

A study by Cohen et al. (2000) of the differences between benign and malignant prostate secretions revealed that benign glands contained CA while cancerous ones did not, but did contain crystalloids and mucin accumulations. In benign glands, CA were present in the lumen of large ducts, with eosinophilic bodies (EB) attached to their surface. Biochemical analysis of CA showed that glycosaminoglycans were the main constituent. Moreover, prostatic secretory cells in benign glands were filled with 1 μm-diameter prostatic secretory granules (PSG). These PSG originated from the Golgi apparatus and contained many of the secreted cell constituents, including enzymes such as prostate-specific antigen (PSA) and prostatic acid phosphatase (PAP) (Cohen et al., 1998). In cancerous glands, these PSG were almost completely absent, and PSA and PAP were dispersed in the cytoplasm of the secretory cells. Together, these findings revealed a dramatic change in the nature of the secretory process in malignant glands. Prostate PSG, EB and CA are both Congo red and PAS positive structures. Prostate CA contained glucosamine, galactose and sulphur, and the monosaccharide/protein ratio was 2:1, while this ratio was 30:1 in PSG (Cohen et al., 2000). The notion that prostate CA arise from urinary proteins (Cross et al., 1992) was discarded, and histological findings as well as the composition suggested that PSG contributed to the formation of CA. In prostatic adenocarcinomas, the inability to form CA seems to stem from the fact that the entire secretory apparatus is absent (Cohen et al., 2000). This suggests that prostatic CA are the final consequence of the apocrine prostatic secretion and the accumulation of cellular remains (Cohen et al., 2000). Milord et al. (2000) found CA in benign reactive prostatic glands adjacent to infarcts. Although CA have frequently been described in benign prostatic acini and rarely observed in adenocarcinoma, Christian et al. (2005) contended that the presence of such inclusions cannot be used to rule out malignancy, as some cancerous acini did contain CA.

The presence of CA in normal and hyperplastic prostatic glands was further studied by Morales et al. (2005). They found that these structures were larger and more numerous in hyperplastic than in normal glands.

In normal glands CA were moderately stained with PAS, while in hyperplastic glands CA were moderately or strongly stained. The study of the expression of glycoconjugates in CA revealed the presence of fucose, mannose, sialic acid, N-acetyl-galactosamine and N-acetyl-glucosamine residues in both normal and hyperplastic glands, with an increase in the four former components in the hyperplastic ones. As these components are also expressed in the glandular epithelium, their results suggested that prostatic CA originate, at least in part, from prostatic secretion.

In 2011, Hammar found CA in prostate gland lumens and highlighted the absence of macrophages around them (Hammar, 2011). Sfanos et al. (2013) reviewed the relationship between infection, inflammation and prostate cancer and stated that CA were remnants of previous prostatic infections and presumably the precursors of calcified stones or prostatic calculi. In fact, an outstanding study by the same authors using high-performance liquid chromatography combined with tandem mass spectrometry demonstrated that the predominant protein components of both prostatic CA and calculi were proteins involved in acute inflammation and, in particular, proteins contained in neutrophil granules. The most prevalent protein was lactoferrin, an iron-binding protein traditionally recognised as bacteriostatic in innate immunity, and other proteins identified were S100 A8 and A9, myeloperoxidase and α-defensins (Sfanos et al., 2009). Moreover, they observed CA engulfed by macrophages and multinucleated giant cells (Sfanos et al., 2009).

Fritz et al. (2010) quantified the components of CA from prostate cancer patients. These structures were found in inflamed glands and the authors suggested that they were associated with age-related prostate tissue remodelling. With respect to their composition, 30–40% consisted of proteinaceous compounds (including mainly S100 A8 and A9), whereas the remainder corresponded to inorganic components comprising hydroxylapatite and whitlockite with high concentrations of Zn^{2+} ions. They reported that Ca^{2+} and Zn^{2+} played a critical role in promoting amyloid(p) assembly of S100 A8 and A9 proteins and formation of amyloid(p) fibrils. Other studies have also reported the presence of S100 A8 and S100 A9 in CA, as well as DNA and proteins from *E. coli* (Yanamandra et al., 2009), and the presence of bacterial "imprints" in prostatic calculi using SEM (Dessombz et al., 2012).

Badea et al. (2015) performed a histochemical and ultrastructural study of the intraluminal content of benign and malignant prostatic tissue. In this study, CA from some patients stained brown with von Kossa staining, indicating the presence of calcium or calcium salts, and some structures were interpreted as transitional forms from CA to prostatic calculi. Furthermore, some CA also stained with autometallography, which labels free or loosely bound heavy metal ions, and with antibodies against PSA. The authors found heterogeneous patterns of intraluminal structures in prostatic acini from the different patients and suggested that this heterogeneity might represent developmental stages of the same type of inclusion, CA or prostatic calculi. Their study also showed the ultrastructure of prostate CA, with fibrillar elements similar to amyloid(p). Kodaka et al. (2008) have also reported that primary prostatic calculi I to III begin from mineralisation of CA as a core, while organic substances that form stone IV might be derived from simple precipitation of prostatic secretions.

A huge study of 355 men with prostate cancer found CA in 84% of cases, in adjacent normal tissue, and this presence was strongly associated with pro-inflammatory factors and with some markers of less aggressive prostate cancer (DuPre et al., 2018). The authors suggested that CA formation might be a normal response to early cancers and could serve to consolidate inflammatory debris and thus prevent more aggressive or mutated tumours. Palangmonthip et al. (2020) also found an association between CA and both concurrent cancer and chronic inflammation. In their study, 75% of all studied prostatic samples showed CA in benign acini, but cancer specimens had a higher incidence of CA in benign acini compared to benign specimens. They concluded that CA was a marker for benign glands but also an indicator that might suggest increased suspicion of concurrent cancer.

A recent study confirmed that prostate CA contained amyloid(p) deposits, as they were stained with Congo red, and the following proteins were identified by mass spectrometric analysis in prostate CA from 46 post-mortem samples: lactoferrin, β2 microglobulin, S100 A9, Ig kappa chain and transgelin (Kanenawa et al., 2019).

2.4. *Corpora amylacea in the respiratory system*

Friedreich was the first to describe intra-alveolar CA in lung, in 1856. He suggested that CA were the product of haemorrhage or exudation into lung tissue, and were composed of a carbohydrate developed by chemical metamorphosis of proteins from extravasated blood (Friedreich, 1856). Later, in 1878, Zahn also noticed CA in the lung, exhibiting a concentric arrangement of layers and a regular, symmetric radial structure (Eastman, 1897). He found various forms of corpora, including round, oval and triangular with rounded corners, and frequently observed a black nucleus, which he took to be a foreign body. He also found bodies in the form of drops which resembled degenerated epithelium and had no detectable radial marking. Zahn proposed that CA were either a product of extravasated blood, as suggested by Friedreich, or of degenerated epithelium. According to Favre, one of Zahn's pupils, the CA could nearly always be found in adults, were formed by the degeneration of mucous membrane epithelium and increased in certain constitutional diseases (Eastman, 1897).

In 1893, Seigert postulated that CA in lung was the product of degenerated epithelium around any possible nucleus (Eastman, 1897). Lubarsch and Plenge (1931) described CA in cases of emphysema, chronic bronchitis, congestion, infarction, atelectasis and pneumonia. Michaels and Levene (1957) studied CA in lungs from 1070 autopsies, and found CA in 3.8% of them. However, CA were not found in samples from people younger than 20 years old, occurred in limited numbers and frequency between ages 20 and 60 and were more frequent after 60 years of age. CA usually ranged from 60 to 100 μm, were found as PAS positive structures and frequently showed alveolar macrophages on their surface.

A rare disorder called *CA pulmonum* was described by Dobashi et al. (1989). In this disease, a solitary mass appeared as an abnormal focus in the lung. In this region, CA were free-floating in the alveolar space and surrounded by exudate alveolar macrophages or multinuclear giant cells. These CA found in lungs appeared as concentrically laminated acellular bodies with a diameter of about 40–80 μm, and were fundamentally composed of fibrillary elements, similar to amyloid(p) fibrils. Moreover, they showed an affinity for Congo red and partial birefringence as well as a strong positivity for PAS reaction. The reactivity for PAS staining was also displayed by the alveolar macrophages and the multinuclear giant cells, which in addition exhibited amyloid(p)-like fibrils in their cytoplasm. This observation led the authors to suggest that CA might be formed by sequential aggregation and compaction of degenerated alveolar macrophages.

Another study found CA in the alveolar spaces of the lung (Röcken et al., 1996). These had a consistently round or ovoid shape with a concentric stratified structure, and most of them showed a rhomboid eosinophilic nucleus. The nuclei were partly black and interpreted to be carbon pigment. Moreover, most of them showed diffuse or ring-shaped staining with anti-Aβ2M antibodies. They were not associated with any other histopathological change in the lung, such as oedema or inflammation. These results suggested that some particles can serve as niduses for the formation of pulmonary CA.

Ohori and Hoff (2008) also indicated that CA in the lungs appeared to be free-floating in the alveoli, showed a Maltese cross pattern with polarisation and presented inclusions in the centre. Some of these inclusions might represent carbon fragments, and the authors concluded that many of these concretions in the lungs formed around small, inhaled particles or other foci of irritation to the alveoli or macrophages. CA have also been described in lung from patients with mesothelioma (Hammar, 2011). These were also found in the alveolar spaces, showing no specific location with respect to the lobe or region of the lung, and

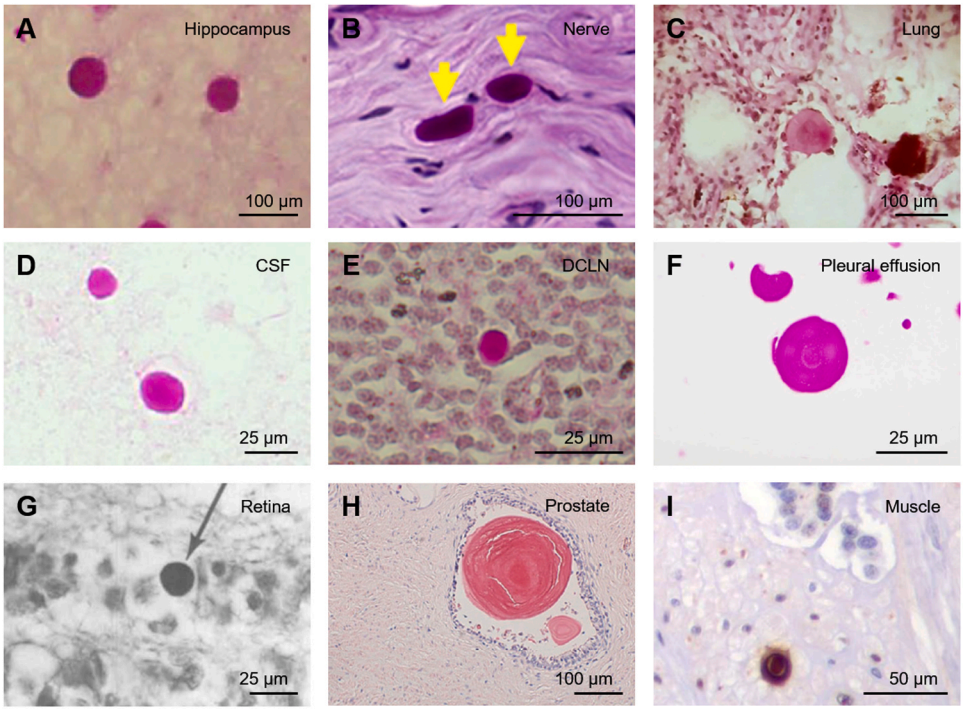

Fig. 1. CA from several human organs and tissues stained with PAS or other stains. A) CA from brain hippocampus stained by PAS (Augé et al., 2017). B) CA from peripheral nerve (intermuscular nerve from quadriceps muscle) stained by PAS-diastase (reprinted from Lu et al., 2016; with permission of Elsevier). C) CA from lung stained by PAS (Gupta et al., 2018). D) CA from CSF stained by PAS (Riba et al., 2019). E) CA from DCLNs stained by PAS (Riba et al., 2019). F) CA from pleural effusion stained by PAS (reprinted from Mani and Wang, 2021; with permission of Wiley Periodicals LLC). G) CA from retina stained by iron staining (reprinted from Avendano et al., 1980; with permission of Association for Research of Vision and Ophthalmology). H) CA from prostate stained by Congo red (reprinted from Kanenawa et al., 2019; with permission of Taylor & Francis Ltd.). I) Intramuscular CA labelled by immunohistochemistry with an anti-ubiquitin monoclonal antibody (reprinted from Hechtman et al., 2013; with permission from BMJ Publishing Group Ltd.).

were surrounded by macrophages. They showed radiating fibrillary lines with delicate circumferential lines under light microscopy, were PAS positive, contained glycoproteins and were free of lipids, calcium and iron. With respect to their shape, they were spherical, elliptical or even rectangular. There were frequent inclusions in the centre of these bodies, such as asbestos bodies or fibres, iron and other particulates and were mostly surrounded by macrophages. The author concluded that CA rid the lung of foreign material.

Numerous CA have also been described in pleural effusion from a patient with systemic lupus erythematosus (SLE) (Mani and Wang, 2021). These bodies ranged between 10 and 92 μm in diameter and were positively stained by PAS, Diff-Quick and Papanicolau staining as well as by haematoxylin-eosin, where they appeared as eosinophilic structures. They were negative for Congo red stain for amyloid(p) and did not contain ubiquitin.

A recent study searched for CA in sputum smears for the first time (Martínez-Girón and Pantanowitz, 2021). They studied 6898 sputum smears from 1075 patients with a range of respiratory diseases, including acute bronchitis, adenocarcinoma, aspergillosis and asthma. Some 1.91% of these smears contained CA, corresponding to 9.7% of the patients. These CA comprised round to oval structures, ranging from 80 to 160 μm in diameter, with a concentric lamellar pattern but no reported nucleus. They were much more frequent in older people and were associated with benign lung diseases. The most frequently observed diseases in the group of patients with CA in their sputum were chronic obstructive pulmonary disease, asthma and congestive heart failure. In contrast, the number of cases of lung cancer with CA in the sputum was very low, leading the authors to conclude that CA are related to non-neoplastic lung diseases.

2.5. *Corpora amylacea in other organs*

CA have also been described in breast, in a primary low-grade marginal zone B lymphoma from a woman with Sjögren's syndrome. These were Congo red and PAS positive and were associated with mammary ductular amyloidosis (Kambouchner et al., 2003). An ultrastructural examination of these CA showed sharply delineated round structures with fibrillary material displaying radial organisation. In any case, CA have only been observed in marginal zone B lymphoma, not in healthy breast, and are thus unusual findings.

Hechtman et al. (2013) described the presence of intramuscular CA adjacent to ileal low-grade neuroendocrine tumours, with a prevalence directly related to tumour size and the presence of carcinoid syndrome. These CA were intracytoplasmic and positive for PAS staining after diastase digestion. They showed the presence of ubiquitin, and a slight positive staining on the periphery for desmin and smooth muscle actin. They measured approximately 7 μm and an ultrastructural analysis revealed a peripheral rim consisting of condensed filaments and a heterogeneous core containing amorphous particles, but the analysis performed by mass spectrometry gave no signals for calcium, iron or other inorganic metals. The authors suggested that CA were the result of a degenerative process, possibly due to chronic myocyte stress caused by the infiltrating, slow growing mass or local hormonal effects.

CA were also found in the gastrointestinal tract, in the lining of cystic spaces of parotid Warthin's tumours (slow growing neoplasms) and were described as a degenerative feature of the tissue together with squamous metaplasia (Webb and Eveson, 2002).

Some uteri from women aged over 84 years old exhibited CA. They were localised in dilated glands of atrophic endometrium and had a slight eosinophilic appearance when stained with haematoxylin-eosin. No nuclei were observed in these CA. They were negative to immunohistochemistry with several anti-amyloid(p) antibodies. In the uterus, CA appeared exclusively in atrophic glands and showed no relationship with amyloid(p) syndromes (Röcken et al., 1996). CA were also found in cervicovaginal smears from healthy fertile women free from any relevant disease, although this finding is not common (Martínez Girón, 2004), and in a woman with *Moluscum contagiosum* (Buckley and Li, 2017). In this latter case, the CA were found physically isolated from the surrounding squamous cells and presented concentric rings arranged in a radial peripheral striation. Although the tissue did not show signs of inflammation, probably due to the patient's history of steroid treatment, the authors suggested that CA might constitute a cervical response to the *Moluscum contagiosum* infection.

Sun (1983) described the presence of CA, as large cytoplasmic inclusions, in the follicular epithelial cells of a thyroid gland with medullary carcinoma, from an old patient. The CA were positive to Congo

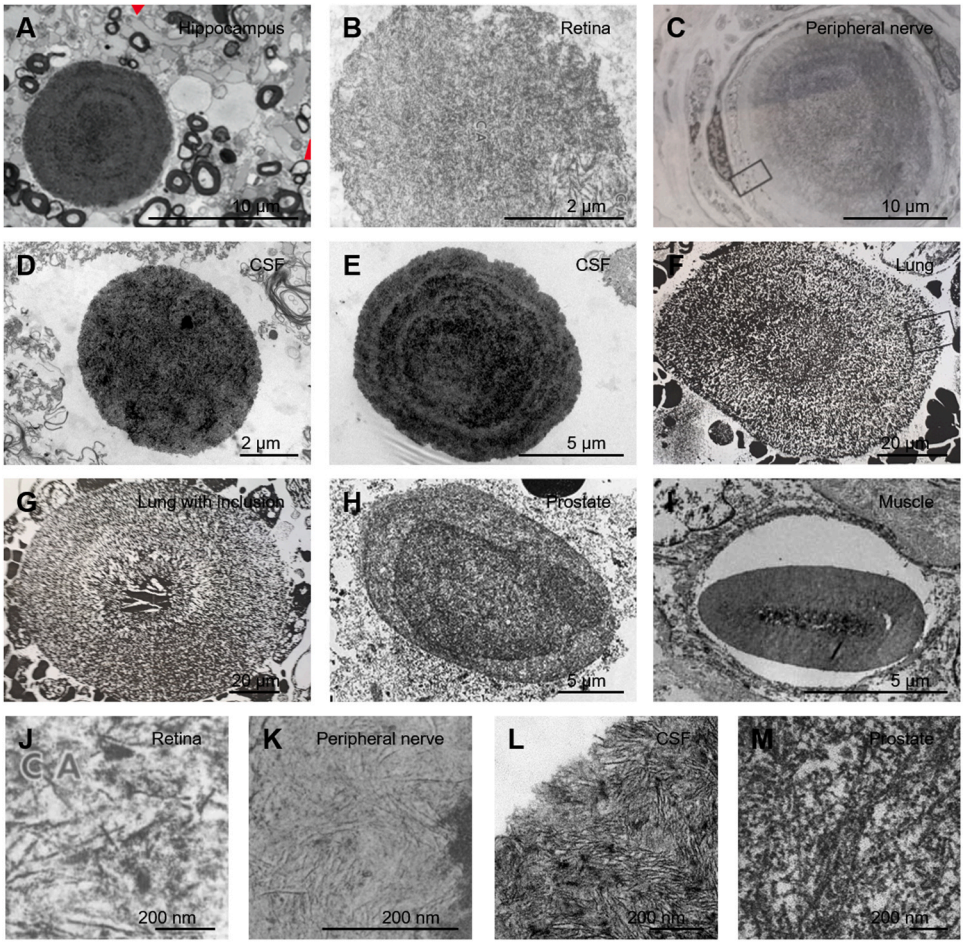

Fig. 2. Ultrastructural images of CA from several human organs and tissues. A) CA from hippocampus (Navarro et al., 2018). B) CA from retina (reprinted from Avendano et al., 1980; with permission of Association for Research of Vision and Ophthalmology). C) CA from a peripheral nerve (sural nerve) (reprinted from Matsumuro et al., 1993; with permission of Springer). D-E) CA from CSF, without (D) and with (E) concentric layers (Riba et al., 2019). F–G) CA from lung, without (F) and with (G) an inclusion in the centre (Dobashi et al., 1989). H) CA from prostate (reprinted from Badea et al., 2015; with permission of Cambridge University Press). I) Intramuscular CA (reprinted from Hechtman et al., 2013; with permission from BMJ Publishing Group Ltd.). J) Inset from B. K) Inset from C. L) Inset from D. M) Higher magnification of a prostate CA (reprinted from Badea et al., 2015; with permission of Cambridge University Press).

red staining, their size varied from 1.5 to 10 µm and their shapes from fusiform to irregular. In addition, fine fibrils were randomly arranged within these inclusions, some of them with poorly defined double strands and rough transverse granularity.

As noted earlier, we also encountered CA in both CSF and DCLNs (Riba et al., 2019). These were PAS positive and contained ubiquitin, p62 and NE that were recognised by natural IgMs. We interpreted them as CA extruded from brain to the CSF, from where some of them reached the DCLNs via the lymphatic system of the meninges. In the case of DCLNs, the CA were attached to a kind of cell which, given their location and form, were probably macrophages.

3. General concerns about CA: discussion and perspectives

As shown in the chronological review, numerous and varied studies have been conducted about CA in different organs and structures, and some of the results appear to be contradictory. However, several features of CA recur in different studies, rendering it possible to obtain a global and inclusive interpretation of these bodies.

Undoubtedly, and as will be discussed below, the most notable feature is that CA have repeatedly been described in every location as accumulating waste products and/or potentially toxic products derived from ageing, pathophysiological conditions, the entry of external material or infectious elements.

However, other features also appear repeatedly. For instance, in all locations, CA have been reported to be PAS positive. Fig. 1 shows representative images of CA stained with PAS from some of these organs. In some structures, such as the prostate, several authors indicated that CA stained with PAS but no images were shown. In these cases, in order to illustrate these bodies in as many organs as possible, Fig. 1 includes images of CA stained with other stains. The fact that CA are positive for PAS staining in all tissues indicates a high polysaccharide content. As shown in the chronological review, early studies of CA in the CNS postulated a high presence of hexoses, predominantly glucose, and related CA to carbohydrate metabolism disruptions (Sakai et al., 1969a, 1969b). However, later studies indicated that brain CA are much more complex than a simple accumulation of glucose polymers resulting from metabolism alterations (Augé et al., 2018a; Riba et al., 2019). In the case of lung, the carbohydrates present in CA have been attributed to the presence of glycoproteins, some of which would have an epithelial origin (Eastman, 1897; Friedreich, 1856; Hammar, 2011). CA observed in peripheral nerve, CSF, DCLNs, breast, muscle and prostate are also PAS positive. In the case of the prostate, it has been observed that sugars can double the amount of proteins, and that this carbohydrate content may include mucopolysaccharides and glucosaminoglycans. Moreover, various monosaccharides have been described in prostate CA, such as mannose, galactose, N-acetyl-glucose and N-acetyl-galactose (Cohen et al., 2000; Morales et al., 2005).

Based on PAS staining, it can be assumed that the CA in different organs and tissues are all amyloid(s) bodies, although it should be noted that this amyloid(s) would reflect the generic presence of carbohydrates rather than starch, and therefore it would be truer to say that CA are glycan rather than starch-like bodies. In the case of the prostate, it is well documented that CA also stain with Congo red, indicating that they contain amyloid(p) proteins as well. Consequently, these CA can be simultaneously considered amyloid(s) and amyloid(p) bodies. Note that most studies of prostate CA use the term amyloid to refer to amyloid(p) content. Meanwhile, although there is little information about them, CA

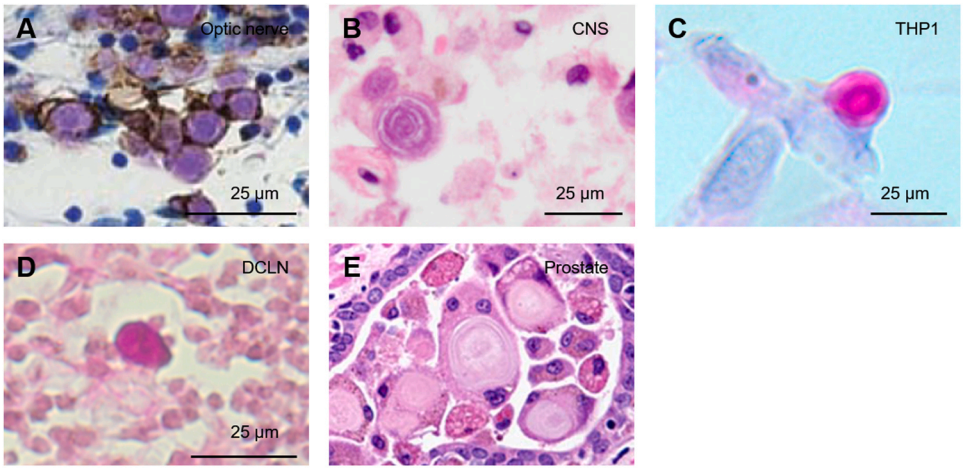

Fig. 3. CA from several organs phagocytosed by macrophages. A) CA from the optic nerve in a NMO-affected region, CA are stained by PAS, and macrophages by an anti-CD68 antibody (reprinted from Suzuki et al., 2012; with permission of Wiley Periodicals LLC). B) CA from basal ganglia stained by hematoxylin-eosin, and macrophages stained by an anti-CD68 antibody (Ohara et al., 2019). C) CA from CSF phagocytosed by THP-1–derived macrophages, PAS staining (Riba et al., 2019). D) CA from DCLNs stained by PAS and surrounded by macrophages (Riba et al., 2019). E) CA from prostate engulfed by macrophages and multinucleated giant cells, hematoxylin staining (Sfanos et al., 2009). Scale bar in E is not provided in the original source.

from breast and in some cases from lung are also described as refringent once stained with Congo red, and therefore may also contain amyloid (p).

Concerning the protein content of CA, the published results seem to be disparate and contradictory. This is partly due to the problem of false positive stainings obtained in immunofluorescence studies. In the case of the CNS, commercial antibodies used in immunofluorescence studies often contain contaminating IgMs that bind to CA. IgMs are recognised by most secondary antibodies, including many that target IgGs, generating false positives that are then reported in articles and give rise to discrepancies (Augé et al., 2017). The problem of false positive immunostaining results has also been observed in studies of prostate CA, such as those on the presence of Aβ2M, which seems to be produced by endogenous biotin reactivity (Cohen et al., 2000). However, other techniques have been used to study CA, such as MALDI-TOF and high-performance liquid chromatography combined with tandem mass spectrometry, and the results confirm that the components of CA are numerous and of varied origin. As detailed in the chronological review, in the case of CA from CNS, proteins of neuronal origin but also substances of astrocytic origin have been repeatedly described, as well as proteins of haematological origin or related to infections. In the case of the prostate, PSA and PAP proteins as well as glycoproteins and aminoglycans have been described in CA, and could be responsible for the amyloidosis observed there (Badea et al., 2015; Cohen et al., 1998). In CA from lung, proteins are mainly part of glycoprotein accumulations, and in those from skeletal muscle, fragments of actin and desmin have been described (Hechtman et al., 2013). Therefore, in view of this disparity of components, it can be concluded that CA are not identical but vary depending on the environment in which they are generated. Consequently, these findings support the notion that CA are structures in which various products derived from different situations are accumulated. Such products may be mainly waste elements, as supported by the fact that CA from CNS, CSF, DCLNs and skeletal muscle contain ubiquitin and p62 proteins, both related to waste substance processing and elimination, and by TEM studies of the ultrastructure of CA.

TEM in human tissue is complex and caution should be observed when interpreting the images obtained because the self-digestion or autolysis of tissue that occurs during post-mortem delay alters its characteristics. Nevertheless, as can be seen in Fig. 2, CA from different tissues exhibit some common features. In general, the ultrastructure of CA shows a dense mass of structures arranged randomly, or in some cases, forming concentric rings, with successive regions of higher and lower densities. The presence or not of concentric rings is not a characteristic feature of a particular organ or tissue, because both configurations are present, for example, in the CSF (Figs. 2D and E). In addition, in some cases, such as lung, a central nucleus interpreted as a foreign body can be seen inside the CA (Fig. 2G). If CA are visualised at higher magnification (Figs. 2J–M), it can be seen that this dense mass often contains fibrillary structures that are tens of nanometres long and a few nanometres thick. Interpretations of these fibrillary structures vary: in some cases, they have been attributed to the carbohydrate component, and in others to fibrillary amyloid(p) protein. In CA from CNS, these fibrillary structures cannot be attributed to amyloid protein because these CA do not stain with Congo red, but in other organs, such as the prostate, some of these fibrils may be amyloid(p). In some of the ultrastructural studies, membranous remains and remnants from cell organelles have been observed close to CA. The presence of cellular debris and the possibility of particles included inside CA further supports the idea that these accumulate waste elements. In addition, the presence of concentric rings has been attributed to different phases or stages of CA growth (Cavanagh, 1999; Dobashi et al., 1989), which could vary according to the rate of waste accumulation and/or the kind of waste products generated.

The idea that CA accumulate waste substances and participate in cleaning processes is also corroborated by the presence, at least in CA from CNS, CSF and DCLN, of NEs that are recognised by natural plasma IgMs. As discussed above, natural IgMs often recognise epitopes that act as markers of residual structures (Reyneveld et al., 2020), and IgM antibodies have been reported to recognise some carbohydrates, such as advanced glycation end products, the production of which increases with ageing (Bovin, 2013; Goldin et al., 2006; Grönwall et al., 2012; Haji-Ghassemi et al., 2015; Lutz et al., 2009; Maddur et al., 2020). Furthermore, our recent studies (Riba et al., 2021) indicate that the NEs present in CA are of a carbohydrate nature. Thus, the presence of NEs in CA may be related to the alterations that occur when waste elements are generated, and NEs may contribute to phagocytosis and elimination of CA. In this regard, CA have often been related to phagocytosis by macrophages. For example, our previous studies have reported that CA in DCLNs are connected to cells whose appearance suggests that they are most probably macrophages (Riba et al., 2019). In addition, in vitro studies have shown that CA isolated from CSF are phagocytosed by macrophages derived from the human THP-1 cell line (Riba et al., 2019). Macrophages have also been found phagocytosing CA in optic nerve from patients with NMO (Suzuki et al., 2012), lung tissue from patients with mesothelioma (Hammar, 2011) and CA from prostate (Sfanos et al., 2009). Fig. 3 shows representative images of CA from different tissues being phagocytosed by or in contact with macrophages.

Despite all these convergent features, other aspects of CA appear to be inconsistent. For example, they can be intracellular or extracellular. In the CNS, there is no doubt that some CA are intracellular. TEM images have shown cell organelles such as mitochondria or vacuolar structures in their vicinity, all surrounded by the cell membrane. In order to detect

the cell membrane surrounding the CA and organelles, the tissue must be especially well preserved and obtained preferably from biopsies or resections, thus avoiding post-mortem delay and tissue self-digestion. In the CNS, the cells that contain CA have sometimes been identified as astrocytes, and it has also been reported that astrocytes can expel CA into the CSF, in an extrusion process that resembles an apocrine secretion (Sbarbati et al., 1996; Riba et al., 2019). In this respect, the presence of matrix metalloproteinase 2 (MMP2) found in the proximity of CA in the CNS could be related to the extracellular remodelling necessary for their extrusion (Augé et al., 2018a). Nevertheless, CA located in the CSF are mainly extracellular. Extracellular CA have also been observed in the alveoli or pulmonary ducts, in pleural effusion, in sputum smears and in the ductular lumen of the breast. It has been proposed that CA from lung derive from epithelial lung cells, and an epithelial origin is also possible in some other tissues or organs. It should be borne in mind that the prostate and the breast, and in general the glandular tissues, contain secretory cells that are of an epithelial nature. Given all this, it is perhaps conceivable that extracellular CA are the result of an apocrine extrusion or secretion of CA formed in certain cells of the surrounding tissues.

At the beginning of Section 3 it was noted that in light of the high carbohydrate content of CA, some authors have suggested that they are products generated simply as a consequence of altered glycogen metabolism (Sakai et al., 1969a, 1969b). However, if this were the case, it would raise questions with no global explanation, and the answers would be inconsistent and unconvincing. For example, if CA were formed as a result of altered glycosidic metabolism, it would be difficult to explain why such a wide variety of products (essentially waste products) have been described in CA. It would also be difficult to explain the presence, at least in some CA, of high amounts of ubiquitin and p62, the former acting as a marker of waste products and the latter as an adaptor for waste processing. In the case of ubiquitin, it should be borne in mind that malin, an E3 ubiquitin ligase, modulates glycogen metabolism in multiple cellular compartments (Gentry et al., 2020). However, in the context of CA it seems difficult to associate ubiquitin solely with glycogen metabolism and not with waste elements. On the other hand, glycogen synthase (GYS) and p62 have mainly been found on the periphery of the CA, whereas ubiquitin is found in peripheral but also central areas, indicating a level of internal organisation of CA. It would also be difficult to explain why CA are generally found in the border areas of the organs or tissues which contain them, and are sometimes found outside these structures. Neither does the metabolic theory explain why some CA are intracellular and others extracellular. Necrosis of CA-containing cells does not appear to explain extracellular CA, as these would be accompanied by significant levels of tissue inflammation and this is not usually the case. Furthermore, the metabolic theory cannot explain the presence of NE in CA (at least in those in CNS, CSF and DCLNs) or the presence of natural IgMs directed against these NE, or why extracellular CA are phagocytosed by macrophages.

Having observed the inconsistencies and weakness of the metabolic theory, it is time to seek another explanation and provide an integrative, all-encompassing hypothesis capable of answering all these questions.

4. Integrative hypothesis regarding CA

Collecting and integrating the results and conclusions given in the studies reviewed above, we propose considering CA in human organs and tissues as waste containers. These waste containers, which are actively created by specific cells, sequester or retain waste products or foreign products, and are then secreted into the external medium or interstitial spaces, in this latter case subsequently being phagocytosed by macrophages. Moreover, as previously posited for CA from brain (Cavanagh, 1999; Riba et al., 2019), we propose that the glycan structure (or part of the glycan structure) is necessary to generate the container skeleton.

In light of this integrated perspective, the time may have come to redefine CA. As noted earlier, the ambiguity of term amyloid, which includes amyloid(p) and amyloid(s), has repeatedly given rise to misinterpretations in studies on CA. Likewise, the concept of CA (corpora "amylacea") has also generated misunderstanding. Consequently, it would perhaps be appropriate to rename CA, and a term such as "wasteosome" (a new term for a body containing waste products) would be more descriptive and would define them more satisfactorily, placing the emphasis on the waste products they entrap, rather than on their amyloid (s and/or p) content.

Wasteosome generation would be intracellular, and would involve the capture of waste elements that may have originated inside or outside the cell, some of which can be marked with ubiquitin and sequestered by p62. Their genesis would also involve the cell machinery necessary for formation of the glycan component that forms the container skeleton. Since the polyglucosan structure containing the wasteosomes or CA from CNS is formed by modified glycogen which resembles that of the polyglucosan bodies found in diseases such as adult polyglucosan body disease and Lafora disease, the machinery involved in their formation might be similar. The aetiology of these diseases includes genetic defects affecting the enzymes that participate in glycogen metabolism, including malin, laforin, glycogen branching enzyme (GBE), glycogen debranching enzyme (GDE) and protein targeting to glycogen (PTG). Thus, these enzymes could be involved in the genesis of the polyglucosan structure that constitutes the CA skeleton. The machinery to form this kind of glycan structure would be physiologically active in cells in which CA are produced, but also in other cells in the case of specific diseases. In such diseases, polyglucosan bodies are found in locations with high glycogen metabolism, such as skeletal muscle and myocardium, and in structures where glycogen metabolism has differential characteristics, as is the case of neurons and retina. It is of interest to note that waste products and the collection of waste elements have not been described in the polyglucosan bodies formed in these diseases, and that we did not find NE in these bodies in a rodent model of Lafora disease (Augé et al., 2018b). Thus, the polyglucosan bodies found in these diseases must be equivalent to the glycan skeleton of CA, and their formation explains the presence of CA-like bodies described in neurons, muscle and other structures. In these diseases, alteration of the glycan metabolism could induce the formation of this kind of glycan skeleton in particular cells. However, alteration of glycan metabolism is not a prerequisite for CA formation. The rate of CA formation may be related to the production of waste elements, which increases with ageing, but also in conditions such as those that involve high levels of oxidative stress. Intracellular waste elements are usually eliminated by specific mechanisms, including the ubiquitin proteasome system and the phagosome/lysosome pathway, but in some cases they may be eliminated through wasteosomes. All the evidence suggests that glycogen or glycogen-like structures can perform the well-known functions of carbon and energy storage and the recently described function of NAcGlc reservoir as a source for N-glycans (Sun et al., 2021), but also the function of coating structures, as in the case of the wasteosome skeleton proposed here.

In addition, we hypothesise that the machinery of wasteosomes would be particularly active in epithelial structures, such as lung epithelial cells and glandular structures (e.g. prostate and breast), in which secretory cells also have an epithelial origin. It would also be active in astrocytes sited near the periventricular margins and in the subpial layer or *glia limitant* of the CNS. Subsequently, wasteosomes would be expelled outside the body or into interstitial areas for their elimination. For example, prostatic CA could be eliminated through the renal system, and CA which are expelled to the CSF or pulmonary ducts could be eliminated through phagocytosis and digestion by macrophages.

Our proposal endows explanations and answers to the previous questions with overall consistency. Because it is based on the presence of waste elements, our theory explains why such a wide variety of products have been described in CA. It also explains why all CA are PAS positive but only some of them are Congo red positive: all CA are PAS positive

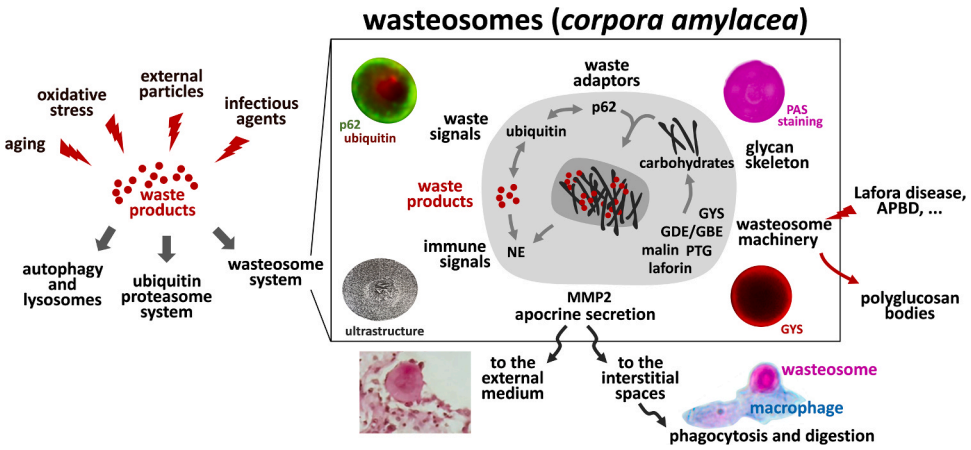

Fig. 4. Wasteosome system: Scheme of the processes involved in the generation and elimination of wasteosomes or CA. Waste products, the production of which increases with age and other circumstances such as those generating an increase in oxidative damage, are usually eliminated via intracellular mechanisms, including the ubiquitin proteasome system and autophagy. In some places, waste elements accumulate to form specific structures known as CA and here renamed as wasteosomes. The genesis of wasteosomes involves the capture of waste elements that may have originated inside or outside the cell, some of which are marked with ubiquitin and sequestered by p62. Their genesis would also involve the cell machinery necessary for the formation of the glycan component that forms the skeleton. This machinery includes malin, laforin, GBE, GDE and PTG. Wasteosomes can be secreted to an external or internal medium, where they are phagocytosed by macrophages. The NE present in wasteosomes might facilitate this process. The aberrant, delocalised activation of the machinery participating in the formation of the skeleton could lead to the formation of particular polyglucosan bodies in other structures, such as those formed in Lafora disease or adult polyglucosan body disease (APBD). See text for details.

because there is a glycan structure, corresponding to the amyloid(s), present in all CA, but only some CA are Congo red positive because only some contain amyloid(p) protein, which accumulates as a waste product. A waste element-based understanding also explains why substances related to infectious processes have sometimes been observed, as well as central nuclei. In addition, our theory explains the reason for the presence and non-random distribution of p62, ubiquitin and GYS. The central part of the CA (containing ubiquitin) would contain an accumulation of waste products, while in the outer part (containing GYS, p62 and ubiquitin), the structure would still be growing and adding new waste products. Concentric rings would be due to non-uniform growth of the CA. Our proposal would also explain why some CA are intracellular and others are extracellular, and why they are mainly found in border areas. Lastly, it also explains why they have been mainly related to ageing, which could be associated with an increase in waste elements.

As a summary of this theory, the processes involved in wasteosome generation and elimination are shown in Fig. 4. A re-reading of the chronological review taking into account this scheme will demonstrate that a high number of observations are coherent with the proposed hypothesis.

CRediT authorship contribution statement

Marta Riba: Conceptualization, Investigation, Writing – original draft, Writing – review & editing. **Jaume del Valle:** Conceptualization, Investigation, Writing – original draft, Writing – review & editing. **Elisabet Augé:** Conceptualization, Investigation. **Jordi Vilaplana:** Conceptualization, Writing – original draft, Writing – review & editing, Supervision, Funding acquisition, Project administration. **Carme Pelegrí:** Conceptualization, Writing – original draft,; Writing – review & editing, Supervision, Funding acquisition, Project administration.

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Declarations of Interest

None.

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