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Oncocytic tumours

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Abstract Oncocytic tumours represent a distinctive set of lesions with distinctive granular cytoplasmic eosinophilia of the neoplastic cells. These cells are called oncocytes because of the "swollen" appearance they have as the result of a striking accumulation of mitochondria. Although generally uncommon, oncocytic tumours are by no means rare and have been reported, with different frequencies, in virtually every organ. A variety of biochemical and molecular changes have been identified, and the aberrant biogenesis of mitochondria in oncocytic cells bears intriguing similarities to that of a group of degenerative disorders known as mitochondrial encephalomyopathies. Although the relationship between the accumulation of mitochondria and the occurrence of tumours is unknown, investigation into the cellular alterations of oncocytes may further our knowledge of a variety of important biological processes such as proliferation, energy production and ageing.

Key words Oncocytic neoplasm · Oncocytic adenoma · Oncocytic carcinoma · Mitochondrial DNA · Oxidative phosphorylation

Introduction

The term "oncocyte" (from the Greek word onkoustai, to swell), first used by Hamperl in 1931 [39], was introduced into the American pathology literature by Jaffe to designate those salivary gland tumours that consisted of oncocytic cells [48]. Cells featuring abundant cytoplasm with a strong affinity for eosin had already been noted in the last century, in the thyroid by Askanazy [4] and in the parathyroid glands by Welsh (Welsh called these cells "oxyphilic") [96].

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The term "Hürtle cell tumour", which is widely used in the American pathology literature to designate oncocytic neoplasms in the thyroid gland, reflects Ewing's incorrect opinion that oncocytic neoplasms originated from the parafollicular thyroid cells described by Hürtle in 1894 [30, 47]. The concept that these cells, with their abundant eosinophilic cytoplasm, share a common denominator regardless of the site of origin should be credited to Hamperl. He not only coined the term "oncocyte" [39], but also correctly suggested that they were the result of some degenerative cytoplasmic alteration and pointed out that they could give rise to tumours with corresponding morphological features – oncocytic tumours [40]. The abnormal increase in the number of mitochondria was not confirmed as the common denominator of oncocytic cells until after the introduction of electron microscopy [27, 61, 74], which demonstrated a variety of morphological changes in the mitochondria of oncocytes, none of which is specific or of diagnostic value [86].

Oncocyte is the generally accepted term for those cells exhibiting the characteristic phenotype, which features in histology sections a finely granular eosinophilic cytoplasm (Figs. 1, 2) and ultrastructurally an increase in the number of mitochondria (Fig. 3). This increase is responsible for the swollen appearance of oncocytic cells. The proportion of cytoplasmic volume occupied by mitochondria has been variably estimated at between 30% and 60% [19, 99]. Incidentally, it is probably useful to distinguish oncocytes from other "mitochondrion-rich cells", such as those described by Tremblay and Pearse in the thyroid [90]. They noted thyroid follicular cells with increased reactivity for mitochondrial oxidative enzymes, but remarked that only oncocytes featured the "highest number of mitochondria" with swelling of the cytoplasm and apparent loss of polarity [90].

The term oncocytosis has been used to designate metaplastic – as opposed to neoplastic – changes featuring the appearance of oncocytic cells. Oncocytic metaplasia is not uncommon in epithelial cells with high metabolic activity (including the endocrine cells or the cells

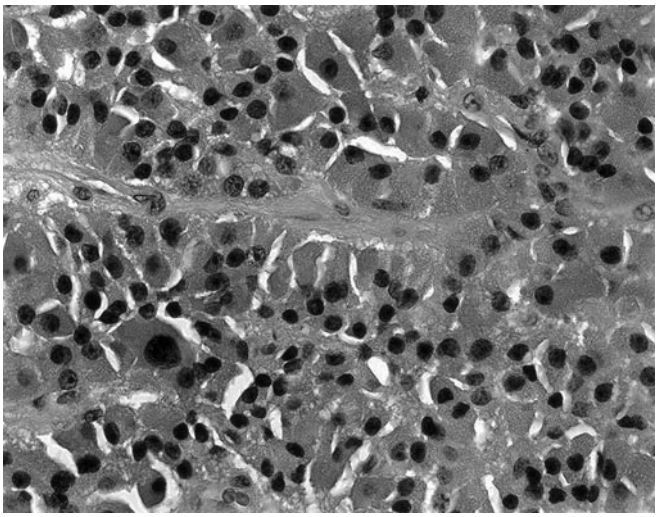

Fig. 1 Histology section of an oncocytic carcinoma of the thyroid gland. The tumour is entirely composed of oncocytes exhibiting abundant finely granular cytoplasm. Oncocytic cells, in addition to the characteristic cytoplasmic changes, feature various degree of nuclear atypia, such as nuclear pyknosis, prominent nucleoli and anisocytosis

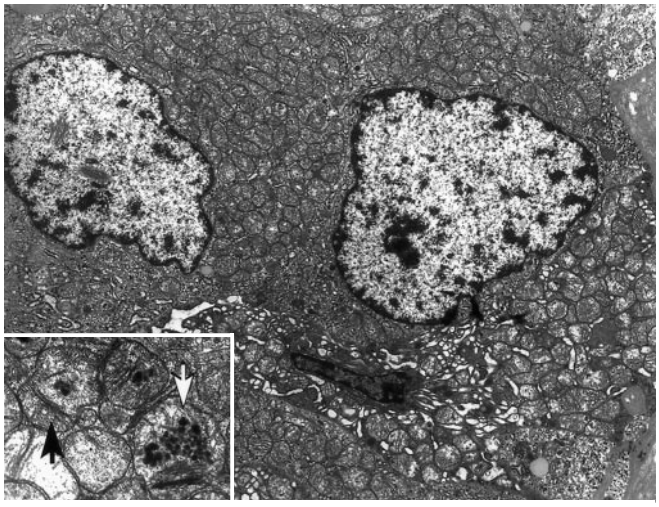

Fig. 3 Electron microscopy of the thyroid tumour shown in Fig. 1. The cytoplasm of tumour cells is filled with contiguous mitochondria. Some of the mitochondria exhibit structural abnormalities, such as stacking of cristae (*inset*, *black arrow*) or dense amorphous inclusions (*inset*, *white arrow*). Although nonspecific, similar structural abnormalities and also accumulation of mitochondria occur in certain types of mitochondrial encephalomyopathies, a class of degenerative neuromuscular disorders

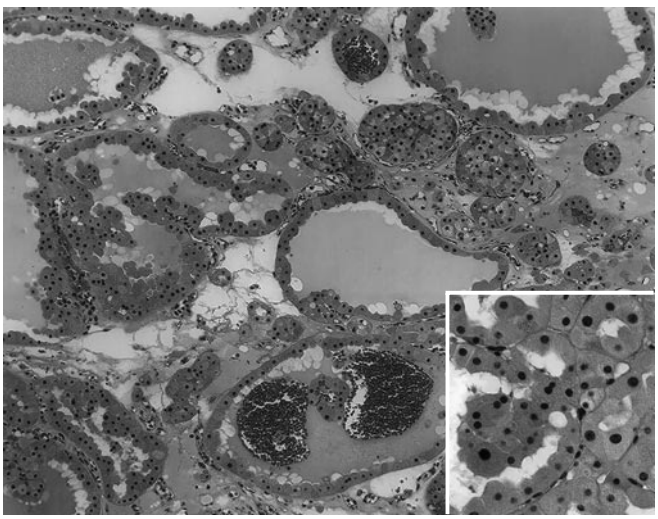

Fig. 2 Histological section of a renal oncocytoma. Nests and variably sized tubular structures composed of oncocytes are embedded in an oedematous stroma. Anisocytosis (*inset*) and nuclear atypia can be seen in otherwise entirely benign renal oncocytomas

of intercalated ducts in the salivary glands) and may be associated with inflammation (Hashimoto's thyroiditis), degenerative processes or cellular ageing [20, 38, 52, 54].

The terms oncocytoma and oncocytic carcinoma are commonly used to designate tumours – benign and malignant – consisting of oncocytic cells. However, the proportion of neoplastic cells exhibiting oncocytic features required to diagnose a tumour as oncocytic seems to vary according to the site of origin. In fact, while it is commonly accepted that thyroid neoplasms with 75% of cells having oncocytic features can be confidently classified as oncocytic [14, 84], stricter criteria are required for a renal tumour to be diagnosed as oncocytic [25]. Despite these apparent discrepancies, few pathologists would argue about classing tumours in which the oncocytic phenotype is the dominant cytomorphological feature as oncocytic neoplasms regardless of strict numerical considerations. In fact, the lack of reproducible techniques to identify mitochondria in histological sections has forced pathologists to rely on the staining qualities of conventional haematoxylin and eosin sections to decide whether a tumour is oncocytic or not. Conventional histochemical stains such as phosphotungstic acid–haematoxylin (PTAH) [55] are relatively easy to perform but not very specific. Several paraffin-reactive antibodies specific for mitochondria have been described [62, 95]. Only recently, however, has a monoclonal antibody become commercially available for routine use on paraffin-embedded material [63]. Such antibodies are proving a useful adjunct to the histological diagnosis [89]. When fresh-frozen tissue is available, enzyme histochemistry may always be used to demonstrate mitochondrial oxidative activity [90] and mitochondria can be directly visualized in living cells with the dye Rhodamine 123 [37].

Pathological and clinical features

With the exception of thyroid and kidney, neoplasms composed of oncocytic cells are generally rare, and it is not clear whether oncocytic lesions such as Whartin's tumour in the parotid or the relatively common oncocytic nodules in the parathyroid gland are true neoplasms.

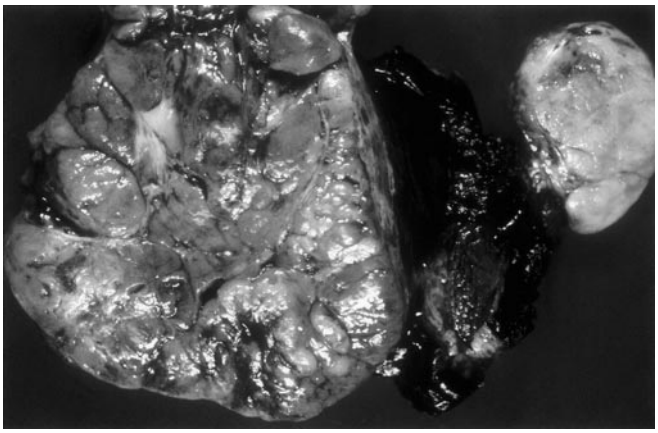

Fig. 4 Gross picture of a thyroid oncocytic carcinoma resected from an 86-year-old woman. The tumour is widely invasive, multinodular and tan-brown, with areas of scarring, haemorrhage and necrosis. The patient is alive with disease (cervical lymph nodes and lung metastases), 2 years after the initial diagnosis

Oncocytic neoplasms in the thyroid gland are a distinct subtype within the group of follicular tumours [73]. The definition of their clinical behaviour has varied. In the 1950s the American Cancer Society was recommending the classification of all thyroid tumours with oncocytic features as malignant [2]. Subsequent studies have clearly demonstrated that – as for any other encapsulated follicular neoplasm – the conventional criteria of vascular and capsular invasion can be successfully applied to predict malignant behaviour [14, 18] (Fig. 4). However, it is important to recognize that the overall mortality rate of oncocytic carcinoma [18] appears to be considerably higher than that of papillary [17] or follicular [53] carcinoma. It is not known whether the increased mortality is related to the intrinsic biological and proliferative properties of oncocytic carcinomas or to decreased competence in iodine-131 uptake [32]. Oncocytic adenomas and carcinomas lacking the nuclear cytological features of papillary carcinoma sometimes have a papillary architecture. These uncommon neoplasms seem to retain the clinicopathological features of Hürtle cell tumours (lower incidence of lymph node metastases and higher disease-related mortality when malignant) [6, 73]. Conversely, a subtype of papillary carcinoma with a distinctive pink cytoplasmic appearance, arising in the background of lymphocytic thyroiditis and with clinical behaviour similar to that of conventional papillary carcinoma, has recently been recognized [3, 9].

Size is an important factor in determining the metastatic potential of renal neoplasms [34], but the large majority of oncocytic tumours in the kidney do not metastasize, regardless of their dimensions. There has therefore been a growing tendency to consider them as benign [25], or extremely low-grade malignant tumours [65] provided that strict morphological criteria are applied [25, 65]. Oncocytomas need to be separated from renal cancers featuring eosinophilic cells with granular cytoplasm. The gross and radiographic appearances of a central stellate scar are by no means diagnostic for oncocytomas, although suggestive of this diagnosis, but can be seen in different types of renal cell malignancy, including chromophobe carcinoma [24] The histological distinction of oncocytomas from the eosinophilic variant of chromophobe carcinoma [88] or renal cell carcinoma with a predominance of granular cells can be difficult in view of the spectrum of architectural, cytological and ultrastructural features in renal neoplasms [87]. Despite the claim of a favourable behaviour, the existence of oncocytomas with atypical morphological or clinical features (such as vascular invasion or perinephric extension) [25, 65], the rare but documented occurrence of metastases [65] and a report of tumours with mixed features of renal cell carcinoma and oncocytoma [25] underscore the importance of thorough sampling and careful pathological examination.

Oncocytic lesions can occur in the salivary glands and are relatively common in the parotid gland, where they are often cystic and associated with a prominent lymphocytic infiltrate (Whartin's tumour). Solid tumours composed of oncocytic cells can also occur in the salivary glands [38]. Rare oncocytic adenocarcinomas have been described in the minor salivary gland [76]. Whartin's tumour is usually regarded as a neoplasm, but may be an oncocytic variant of the benign lymphoepithelial cysts found in the parotid gland and one of a spectrum of similar lesions found in the head and neck region [82].

Cells with oncocytic features (oxyphil cells) are normally present in the parathyroid gland, where they first appear around puberty, increase in number with ageing and are often arranged in discrete nodular collections [74]. A variable proportion of oncocytic cells is also present in both adenomatous and hyperplastic parathyroid nodules and the term oncocytic should therefore be restricted only to those lesions that are composed virtually entirely of oncocytic cells. When strictly defined, oncocytic adenoma is estimated as representing under 5% of all parathyroid adenomas associated with hyperparathyroidism [98]. The distinction between small nonfunctioning adenomas and age-related nodular aggregates of oncocytic cells may be impossible. Oncocytic carcinomas of the parathyroid gland are a rare occurrence but have been documented in the literature [60].

Fibrolamellar carcinoma, also known as fibrolamellar oncocytic hepatoma or oncocytic hepatocellular tumour, is an uncommon but well-documented example of a primary oncocytic neoplasm of the liver. It is considered a variant of liver cell carcinoma and features distinctive morphological (neoplastic hepatocytes with oncocytic change and fibrosis) and clinical characteristics (favourable prognosis, occurrence in a young patient population, lack of association with cirrhosis) [23, 78].

Oncocytic change is known to occur in the normal adenohypophysis [52] as well as in pituitary adenomas. The term pituitary oncocytoma is generally used to mean only those tumours with widespread oncocytic change. As a rule, these tumours are not associated to any signifi-

cant hormone production and are therefore regarded as a subtype of null cell adenomas [51]. Oncocytic neoplasms have also been described in other endocrine glands, such as the adrenal gland and the ovary [29, 66, 100].

Neuroendocrine tumours with oncocytic features are well documented at various sites originating from the embryonal foregut, including the larynx [81] and the lung (oncocytic carcinoids) [77], but also in the pancreas [70] and in the thyroid as a variant of medullary carcinoma [42].

Oncocytic neoplasms also occur in the sinonasal region [7, 41] and in the lung [31]. An intraductal oncocytic tumour of the pancreas with distinctive papillary architecture and low-grade malignant behaviour has recently been recognized [1]. Lesions featuring oncocytic cells are known to occur in the larynx (ventricular cysts [13, 35] and in the ocular adnexa (in particular the caruncle and the lacrimal sac [10, 64]. Rare oncocytic tumours have also been described in the breast [22] and in the prostate gland [8]. Recent reports, all including the results of ultrastructural examination, have documented the occurrence of oncocytic neoplasms in the skin [75], soft tissues [67], the haematolymphoid system [12] and the meninges [72]. The oncocytic variant of meningioma has been associated with a relatively aggressive behaviour [72].

Unravelling the pathogenesis

In addition to the characteristic morphological alterations, a variety of molecular and biochemical changes have been described in oncocytic tumours. For instance, DNA content profiles after flow cytometry are commonly abnormal. Thyroid oncocytic neoplasms, including histologically benign tumours, are often aneuploid [15, 49], a finding that parallels the common occurrence of nuclear atypia and anisocytosis on histological sections [84] (Fig. 1). The demonstration of aneuploid or polyploid DNA content in thyroid oncocytic tumours does not help in differentiating adenomas from carcinomas [15]. It has however, been suggested that in those thyroid tumours that are histologically malignant (associated with capsular or vascular invasion), aneuploidy might be a marker for a particularly aggressive clinical behaviour [15, 71]. Renal oncocytomas may also show abnormal DNA content [71].

A fair number of renal oncocytomas has been analysed by conventional cytogenetics and comparative genomic hybridization demonstrating at least two subgroups of tumours: those with loss of chromosomes 1 and Y and those with rearrangements involving 11q13 [59, 69, 92]. In general, oncocytomas exhibit few karyotypic alterations compared with renal cancers [69] and cytogenetic analysis is helpful in the differential diagnosis since the former lack chromosomal deletion at the site of the von Hippel-Lindau gene on the short arm of chromosome 3, which is the hallmark of renal cell carcinoma [68].

Restriction fragment length polymorphism (RFLP) analysis demonstrated that unbalanced losses of genetic material are relatively more common among thyroid than among renal oncocytic neoplasms, in keeping with their greater malignant potential [85]. Loss of heterozygosity from the long arm of chromosome 10 was the only genetic alteration detected by RFLP in both thyroid and renal oncocytic tumours and may therefore be pathogenetically relevant [85].

Skeletal muscle cells in patients with mitochondrial encephalomyopathies [26] may exhibit what could be considered a particular type of oncocytic metaplasia. This class of degenerative neuromuscular disorders was initially defined on the basis of ultrastructural alterations in the mitochondria of the skeletal muscle cells of the affected patients. Sometimes mitochondria accumulate in large aggregates and display a variety of morphological alterations, including abnormal cristae and inclusions. Although the morphological changes in the mitochondria are nonspecific, similar alterations have been described in oncocytic neoplasms [86] (Fig. 3). Histologically, the aggregates of mitochondria are easily visualized by a modified Gomori stain as purplish patches giving the skeletal muscle cells a characteristic ragged-red appearance [26]. The effort to characterize the biochemical and genetic defects involved in mitochondrial encephalomyopathies has resulted in significant advances in our understanding of the physiology and pathology of mitochondria and in a more specific definition of this class of neuromuscular diseases [79]. Loss of function of key components of the oxidative phosphorylation process as a result of mitochondrial DNA (mtDNA) abnormalities such as point mutations or deletions often represents the underlying biological defect [79] and may result in a compensatory increase of mitochondria in the myopathies with ragged-red fibres [26]. Cases of infantile oncocytic (histiocytoid) cardiomyopathy are also characterized by abnormal accumulation of mitochondria in the cardiac myocytes [11, 33, 56, 80], and it is likely that similar mtDNA alterations are the underlying genetic abnormality in at least a proportion of cases. One of the patients with infantile oncocytic cardiomyopathy featured a set of systemic pathological abnormalities with oncocytic change in the endocrine glands [80].

Mitochondrial DNA comprises less than 1% of the total DNA in eukaryotic cells but is a distinct species with its own genetic code and a circular molecular structure similar to that of a plasmid. In humans, mtDNA molecules are 16,569 bp long, and it is estimated that there are 2–10 mtDNA molecules per mitochondrion. The entire sequence of mtDNA has been characterized [93] and encodes for 13 proteins (all essential components for the mitochondrial oxidative phosphorylation process), 2 ribosomal RNA (rRNA) and 22 transfer RNA (tRNA). Both rRNAs and tRNAs are specific for mitochondrial protein synthesis, which is at least in part independent of that occurring in the cytoplasm of eukaryotic cells [5, 79]. This is in keeping with the hypothesis that mitochondria are the result of endosymbiotic evolution of

bacteria specialized in oxidative phosphorylation within eukaryotic cells. During philogenesis, however, control of the respiratory function has been progressively taken over by the nuclear genes which in humans encode for 90% of the mitochondrial respiratory chain proteins and for the enzymes necessary for mtDNA replication and transcription [5]. There are other characteristic features of the mitochondrial genome are. (1) Few noncoding sequences (introns) are present [93]. (2) Replicative segregation in the dividing cells of an organism, with a threshold for phenotype expression that is dependent on the number of mtDNA molecules with the specific mutant marker within a given cell [79]. (3) Its inheritance is maternal, since mitochondria are inherited through the oncocyte (it is estimated that under 0.1% of the mitochondria are contributed by the sperm at fertilization) [36]. (4) It has naturally occurring polymorphic sequences, which are valuable tools for population genetic analysis [16]. (5) The copy number is higher (1000–10,000) than for nuclear genes which are present as only two alleles in the dipoid cell; this makes mtDNA polymorphism particularly suitable for forensic identification of human remains, including bone fragments or partially decomposed tissue [44]. (6) Unlike nuclear DNA, mtDNA molecules are not protected by histones and other proteins. In contrast, they are exposed to the damaging effect of oxygen free radicals, a natural by-product of mitochondrial oxidative phosphorylation. As a result, mtDNA has a high mutation rate, estimated at approximately 10 times that for nuclear DNA [79].

A variety of diseases such as ischaemic heart disease, late-onset diabetes mellitus, Alzheimer's disease, Parkinson's disease and Huntington's disease, have been associated with mtDNA alterations analogous to those found in the mitochondrial encephalomyopathies [94]. In fact, large mtDNA deletions (such as the one of approximately 5,000 bp designated mtDNA^{4977}), which are present at high levels in several mitochondrial encephalomyopathies [79], seem to accumulate progressively in ageing normal tissues [21], and it has been suggested that ageing and age-related degenerative disease might be the result of a decline in oxidative phosphorylation capacity caused by the accumulation of mtDNA deletions [57, 94].

Although the type of cellular derangement(s) causing the abnormal accumulation of mitochondria in oncocytic neoplasms is obscure, there are important features in common with mitochondrial encephalomyopaties, including some of the ultrastructural alterations of the mitochondria [86]. Numerous key components of the oxidative phosphorylation machinery have been identified histochemically or immunohistochemically in oncocytic lesions of the thyroid, kidney, parathyroid gland and salivary gland [28, 46, 58, 62, 90], but only a partial deficiency of cytochrome-C-oxidase in oncocytic nodules of hyperplastic or adenomatous parathyroid glands has been found [58]. Oncocytes have traditionally been regarded as cells with active metabolism and high levels of oxidative enzymes [90]. However, this does not appear to correlate with adequate cellular performance and, at least in the thyroid gland, oncocytic cells exhibit decreased iodide uptake [32], reduction in the total protein and in the thyroglobulin content, and lower peroxidase and iodination activity with poor iodination of thyroglobulin [91]. These findings suggest a defect in the energy production machinery of the cell and indicate that the increased mitochondrial content is compensatory. However, proteins uncoupling the oxidative phosphorylation process, such as those physiologically expressed in the brown fat are not present in oncocytic tumours [28]. Alterations of mtDNA may underly the deficit in energy production and result in the abnormal accumulation of mitochondria, but the existence and the relevance of specific mtDNA alterations in oncocytic neoplasms require further investigation [28, 85, 97]. The mtDNA^{4977} associated with cellular ageing is present in oncocytic neoplasms [85], but it has also been detected in the adjacent non neoplastic tissue and represents only a low proportion of the total mtDNA content in both thyroid and renal oncocytic tumours [85]. That this and other large mtDNA deletions are unlikely to play a major part in the development of the oncocytic phenotype is consistent with the general detection of functional activity of the oxidative phosphorylation complexes [28, 90], with the lack of identifiable abnormal mtDNA species after restriction endonuclease analysis and Southern blotting [28, 85] or sequential amplification of the entire mitochondrial DNA [85]. However, the occurrence of relatively small mtDNA deletions cannot be ruled out. In fact, although a rare occurrence, a novel mtDNA deletion involving the oxidative phosphorylation complex I has been detected in renal cell carcinoma [45]. Preliminary results of the screening with allele-specific oligonucleotides of oncocytic tumours for specific mtDNA point mutations known to be associated with a variety of mitochondrial disorders has revealed base substitutions in several thyroid and renal oncocytic neoplasms. However, these were also detected in the corresponding nonneoplastic tissue, and their role is unclear [50]. The abnormal accumulation of mitochondria in oncocytic tumours is associated with a 4- to 5-fold increase in mtDNA in both renal and oncocytic neoplasms [85]. This increase is not accompanied by a parallel rise in mitochondrial RNA transcripts [83], despite the enhanced expression of nuclear genes involved in the mitochondrial oxidative process to parallel the increased mtDNA levels and abnormal accumulation of mitochondria [43]. These findings are compatible with poorly functioning or nonfunctional mitochondria in oncocytic neoplasms and suggest that the excess of mitochondria may be the result of a partial block of RNA transcription in the mitochondria or of decreased RNA stability. Alternatively, the relative decrease in mitochondrial transcript levels might result from feedback signals inhibiting the uncontrolled production of RNA transcripts should the abnormal accumulation of mitochondria be driven by alteration(s) of the nuclear genes which normally control the replication of mitochondria.

In conclusion, although the biogenesis of mitochondria in oncocytic cells is obviously abnormal and its relationship to the development of tumours still obscure, the importance of the biological processes involved justifies the study of the cellular alterations in oncocytic lesions. These may represent a valuable model and investigation of their aetiology may contribute to a better understanding of complex and diverse cellular functions such as proliferation, regulation of energy production and ageing.

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