Oncocytic lesions of the ocular adnexa: A review of the histopathology with a brief discussion of the pathogenesis

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Abstract:

Oncocytic lesions may be metaplastic, hyperplastic, or neoplastic and occur in a variety of tissues, including those of the ocular adnexa. Oncocytes are enlarged epithelial cells with abundant eosinophilic granules in the cytoplasm, which represent large mitochondria with distorted cristae. The causes of oncocytic lesions remain uncertain, although in some sites such as the lacrimal sac, chronic inflammation may be a factor. Oncocytic neoplasms in all adnexal sites are generally benign (oncocytoma/oncocytic adenoma) and oncocytic adenocarcinomas are uncommon. Research into oncocytic neoplasms, particularly of the kidney and thyroid, has shed some light on the complicated genomic and metabolic changes that are associated with mitochondrial dysfunction in such neoplasms. The major driver event is mutation of mitochondrial DNA-encoding subunits of complex I in the respiratory chain. The subsequent metabolic events may promote tumorigenesis and inhibit malignant transformation. This review discusses the histopathology and histogenesis of two examples of oncocytoma in the ocular adnexa and presents a simplified synopsis of the genomic and metabolic changes that are significant in the pathogenesis of these neoplasms.

Keywords:

Caruncle, lacrimal sac, mitochondria, mtDNA mutations, oncocytic tumors

INTRODUCTION

The current understanding of an oncocyte as a transformed epithelial cell was established by Hamperl in 1962.[1] These cells are of increased size compared to the cells of origin, with a variable, but generally large, number of eosinophilic granules in their cytoplasm that represent abnormal mitochondria. The cells show variable loss of specialized cytoarchitectural features and look similar in all sites, a manifestation of convergent differentiation. Oncocytes are seen normally in the parathyroid glands, occurring more frequently with advancing age, and may also be seen in other endocrine and exocrine glands. Importantly, oncocytic transformation does not prevent cell division and neoplasms of oncocytes, designated oncocytomas, are seen in a variety of locations, including the kidney, the thyroid gland, salivary glands, and the ocular adnexa.

In 1977, Biggs and Font collected 18 cases of periocular oncocytic lesions from the files of the Armed Forces Institute of Pathology for review and added a further 17 cases from the literature.[2] Of the 35 cases, 19 (54%) arose in the caruncle and 8 (23%) arose in the lacrimal sac. The remaining tumors were found in the conjunctiva, the eyelid, and the lacrimal gland. Three cases were deemed to be malignant: two in the lacrimal gland and one in the lacrimal sac. In this review, we present the clinical features and histopathology of oncocytomas in the caruncle and lacrimal sac and review the literature on the pathogenesis of these tumors.

CASE REPORT 1

A 70-year-old man presented with a prominent and chronically inflamed left caruncle [Figure 1]. Excisional biopsy yielded a specimen of membranous tissue measuring 7 mm in maximal dimension with yellowish nodules beneath the mucosal surface. Microscopic examination revealed normal caruncular surface epithelium

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with numerous goblet cells and a cystic structure in the substantia propria lined by large epithelial cells with granular eosinophilic cytoplasm [Figures 2 and 3]. Normal ducts and acini of accessory lacrimal gland tissue were seen adjacent to the cyst. There were additional collections of ducto-acinar structures lined by oncocytes and the substantia propria contained scattered collections of lymphocytes and plasma cells [Figure 2]. A definite connection to the surface epithelium was not identified. A pathological diagnosis of caruncular oncocytoma was made. There has been no recurrence.

CASE REPORT 2

An 87-year-old woman presented with a 6-month history of right chronic dacryocystitis and epiphora. A large swelling over the right lacrimal sac had been present for 3–4 years. With a clinical diagnosis of dacryocystocele, a dacryocystorhinostomy was performed, revealing a large mass apparently extending into the anterior orbit. This was removed and an ethmoidectomy was carried out.

The wound healed well, but a computed tomography scan 3 months postoperatively revealed a soft tissue lesion, 23 mm in maximal dimension, extending along the nasal wall with some destruction of the bone. This was thought to be a recurrence of the tumor, and the patient underwent complete excision of the right lacrimal drainage system. The tumor appeared to be entirely contained within the lacrimal sac, but an inferior turbinectomy was performed because of concern about possible tumor in the nose. There was no further recurrence.

The original excisional biopsy consisted of multiple pieces of firm tan tissue with a papillary configuration, the largest measuring 17 mm in maximal dimension. Microscopically, the specimen proved to be an epithelial tumor composed of cells with eosinophilic and finely granular cytoplasm, round-to-oval nuclei with finely dispersed chromatin, and solitary, prominent nucleoli, consistent with oncocytes. The growth pattern was mixed with solid and trabecular areas, as well as numerous tubules lined by tall columnar oncocytes overlying cuboidal

basal cells [Figure 4]. Periodic acid–Schiff-positive mucin was present in many of the lumina. In some of the areas with a more solid growth pattern, spindled cells were present [Figure 5]. Collections of oncoblasts were scattered throughout the tumor. There was a focal desmoplastic reaction but no definitely invasive growth pattern. A few mitotic figures were identifiable, but nuclear atypia was mild, and there was only one small focus of necrosis. Vascular permeation and perineural infiltration were not seen. Ultrastructural examination confirmed the oncocytic nature of the tumor: the cytoplasm was packed with large mitochondria with aberrant cristae. A pathological diagnosis of benign oncocytoma with atypical features was made.

The recurrent tumor was confined to the lumen of the lacrimal sac and did not involve the canaliculi or the nasolacrimal duct. Tissue from the nose did contain oncocytoma, although the nasal mucosa was normal. Although the origin of the tumor was not identifiable, areas of sac epithelium showed oncocytic metaplasia [Figure 6]. Mitotic activity and cytological atypia were not seen.

DISCUSSION

Since the review of Biggs and Font identified the caruncle as the most common location for periocular oncocytomas, there have been numerous case reports and studies that have highlighted the clinical features.[2] Nevertheless, the tumor is rare in this site. In a recent review of 218 caruncular tumors seen over 40 years by an ocular oncology service, there were only 4 oncocytomas (1.8%), a figure that tallies well with previous reports where the proportion of oncocytomas among caruncular lesions ranged from 0% to 5.1%.[3,4] Although there are exceptions, these unilateral tumors are generally seen in older patients (>60 years) and most are slow growing with a maximal dimension <10 mm.[5,6] They have a tan-red or bluish color and are usually asymptomatic. They are often cystic and
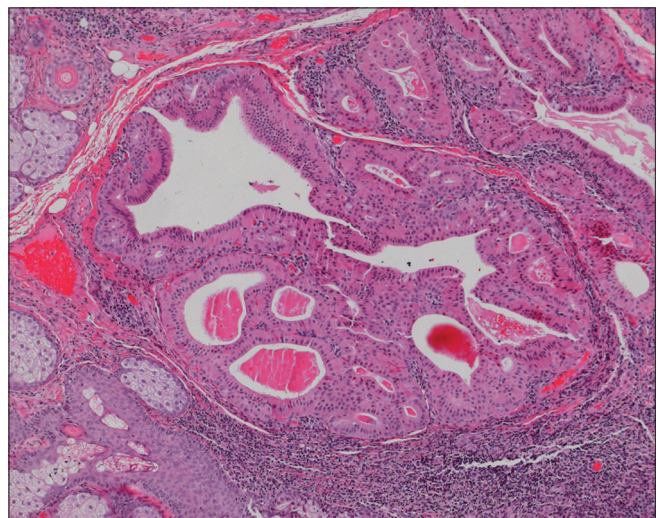

Figure 1: Clinical appearance of enlarged left caruncle containing partially cystic oncocytoma

Figure 2: Small portion of caruncular cyst with ducto-acinar elements lined by oncocytes and adjacent lymphoplasmacytic infiltrate (Hematoxylin and eosin; original magnification, ×100)
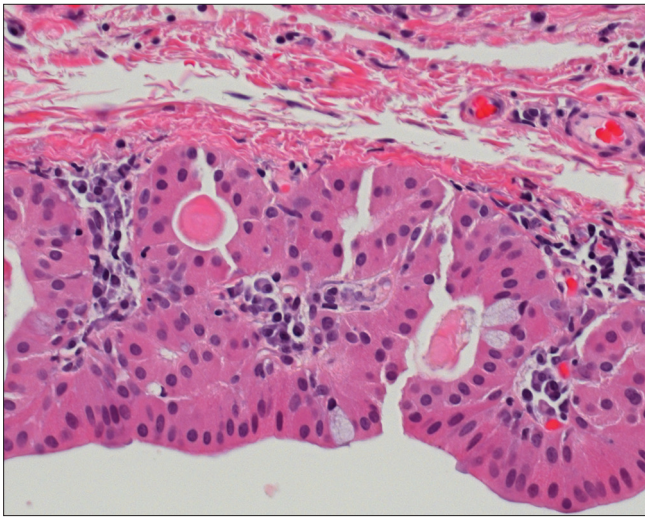
Figure 3: Cyst lining of enlarged cells with regular nuclei and eosinophilic granular cytoplasm. The lining epithelium contains a few scattered goblet cells (Hematoxylin and eosin; original magnification, ×400)

Figure 4: Tubular area of lacrimal sac tumor with columnar oncocytes overlying cuboidal basal cells (Hematoxylin and eosin; original magnification, ×100)

the proteinaceous contents of the cysts may cause the tumor to appear pigmented.[7,8] Malignant cases have not been described and simple excisional biopsy is curative.[4]

Biggs and Font described oncocytic metaplasia of both conjunctival surface epithelium and accessory lacrimal gland ducts in their cases of caruncular oncocytoma.[2] Subsequent authors have favored an origin from metaplastic epithelium in the ducts of accessory lacrimal glands on both histological and immunohistochemical grounds and the presence of scattered goblet cells within the epithelium is consistent with a ductal origin.[9-11] Others have favored an origin from seromucinous glands, at least in the lacrimal sac, where such glands have been described in the inner wall.[12]

Despite this knowledge, there is still no clear understanding of what stimulates the development of an oncocytoma. Given that the tumor generally arises in older people, an early view was that the swelling of the epithelial cells was a degenerative change. Alternatively, some form of metabolic derangement might account for the frequency with which the tumor arises in metabolically active tissues such as the kidney and exocrine and endocrine glands. A causative role for inflammation is a third possibility. Biggs and Font and Heathcote *et al.* noted a scanty lymphoplasmacytic infiltrate in some cases of caruncular oncocytoma and Østergaard *et al.* identified inflammation in 62% of their cases.[2,10,11] However, in the caruncle, the evidence for an inflammatory cause is weak at best.

In the thyroid gland, oncocytic metaplasia of follicular epithelium is one of the defining pathological features of Hashimoto's thyroiditis and a stronger case for the role of inflammation can also be made for the lacrimal sac. Chronic dacryocystitis is a relatively common condition, and although sac mucosa is not routinely sampled at dacryocystorhinostomy, oncocytic metaplasia has been identified in 5% of mucosal biopsies.[13] The metaplastic change
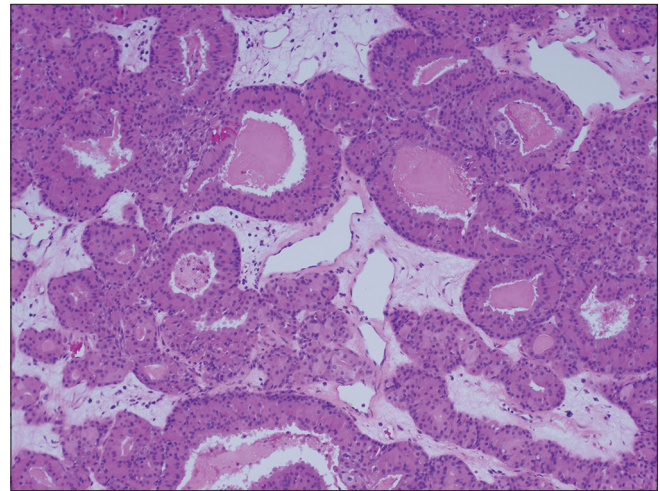
can be identified in the epithelium lining the crypts of the sac, which may proliferate to produce a glandular structure, thereby mimicking the process of branching morphogenesis that occurs in the embryological development of salivary glands [Figure 7].[14] A number of authors have described the occurrence of an oncocytoma in the lacrimal sac of patients with chronic dacryocystitis.[15,16] In a series of 498 lacrimal sac specimens obtained at dacryocystorhinostomy or dacryocystectomy, Alkatan and Al-Qurashi identified seven oncocytomas, all of which were benign.[16] One of the four cases of oncocytoma arising in the lacrimal sac identified by Pe'er *et al.* had a lymphoid stroma similar to that seen in Warthin's tumor of salivary gland.[12]

Most, but not all, patients with oncocytomas in the lacrimal sac present with epiphora. Unilateral epiphora resulting from nasolacrimal duct obstruction by an oncocytoma arising on the inferior nasal turbinate has been described, emphasizing the value of nasal endoscopy if there is a suspicion of a tumor in the lacrimal drainage system.[17,18]

Although oncocytic metaplasia of ductal or sac epithelium is easy to recognize, the histopathological criteria for other possible oncocytic lesions are not so well established. In their series of 18 cases, Biggs and Font described one case of oncocytic hyperplasia and one case of oncocytic adenomatous hyperplasia; in neither case were diagnostic criteria defined.[2] Østergaard *et al.* used criteria previously applied to oncocytic lesions of salivary gland: hyperplasia was characterized by nodular/cystic foci of oncocytes with oncocytic adenomas (oncocytomas) being larger, more circumscribed, and at least partially encapsulated.[11] Among their 34 cases, there were 26 adenomas, 4 cases of hyperplasia, and 4 cases of metaplasia. It is by no means clear that these criteria can be applied consistently or that the distinction between hyperplasia and adenoma is meaningful. No examples of oncocytic adenocarcinoma
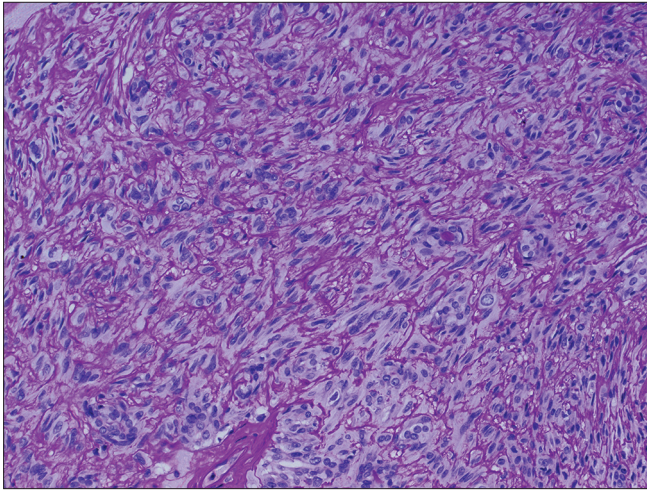
Figure 5: Solid area of sac tumor with spindled oncocytes. Nests of spindled oncocytes are outlined by periodic acid–Schiff-positive matrix and show mild nuclear atypia (Periodic acid–Schiff stain after diastase treatment; original magnification, ×200)
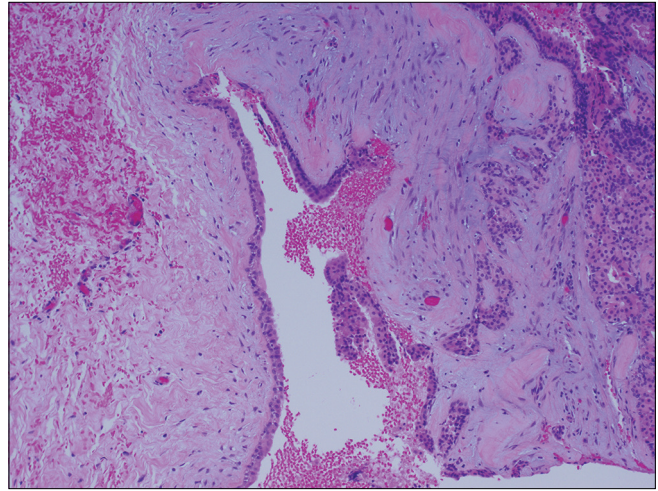

Figure 6: A crypt of lacrimal sac showing oncocytic metaplasia of the surface epithelium. The wall of the sac is scarred and contains collections of oncocytes in a pseudo-infiltrative pattern (Hematoxylin and eosin; original magnification, ×100)

arising in the caruncle have been published, and the malignant form of oncocytoma is rare in the lacrimal sac. In a review of 115 lacrimal sac neoplasms, Stefanyszyn *et al*. identified 4 oncocytomas and 44 malignant epithelial neoplasms, of which 2 were oncocytic adenocarcinomas.[19] Histopathological diagnosis of oncocytic adenocarcinoma of the lacrimal drainage system requires demonstration of destructive infiltrative growth with lymphovascular permeation and perineural infiltration, as well as oncocytes demonstrating nuclear atypia in small nests and abortive glandular elements; mitotic figures may be uncommon.[20,21] One case of an oncocytic adenocarcinoma of the sac presenting with cervical nodal metastases has been reported.[22] There have been at least two reports of benign sac oncocytomas undergoing transformation into oncocytic adenocarcinoma, one of which initially recurred as an oncocytoma with atypia.[23,24] Mikkelsen *et al*. reviewed 13 cases of oncocytoma of the lacrimal gland in the literature, none of which recurred or underwent malignant change.[25] It would appear likely that most oncocytic adenocarcinomas within the ocular adnexa arise *de novo*.

In a comprehensive review of renal oncocytoma, Trpkov *et al*. reviewed the frequency and significance of atypical microscopic features, including nuclear atypia, mitoses, and the presence of small cells with scanty cytoplasm and dark nuclei, lacking nucleoli, which they designated as oncoblasts.[26] They found that these atypical features were not associated with an increased rate of recurrence, progression, or death in this organ. Case no. 2 above illustrates that oncocytomas in the lacrimal sac can also display several of these concerning histological features (nuclear pleomorphism, distorted tubular structures, spindling of cells, and readily recognizable mitoses) without being frankly malignant. In our case, the tumor did recur rapidly, but the atypical findings were not observed in the recurrence.

The histopathological diagnosis of oncocytoma in any tissue is relatively straightforward and does not usually require ancillary tests. The presence of numerous eosinophilic granules in the cytoplasm of large epithelial cells is generally indicative of the accumulation of endoplasmic reticulum, lysosomes, or mitochondria and the presence of the latter can be confirmed if necessary with Mallory's phosphotungstic acid hematoxylin, which stains the mitochondria blue, or transmission electron microscopy.[10] Cytoplasmic eosinophilia may be quite variable, possibly reflecting variable accumulation of abnormal mitochondria.[27] More recently, the antimitochondrial antibody Mu213-UC has become available.[11] Although the oncocytic cells express a range of cytokeratins characteristic of lacrimal gland ducts (CK5/6, CK7, CK8/18, CK19, and to a lesser extent, CK14), there is no specific immunophenotype of diagnostic value.[11]

The classical pathology of oncocytoma described above has been recognized for decades, but several questions remain.
- What causes accumulation of the mitochondria?
- What causes the morphological abnormality of the mitochondria?
- Is the morphological abnormality indicative of mitochondrial dysfunction and what is the effect on cellular metabolism?
- Why are oncocytic neoplasms, for the most part, benign?

With the increased understanding of mitochondrial function and genomics over the past 20–25 years, some of these questions have begun to be answered. Research into the molecular pathogenesis of oncocytic neoplasms has largely been carried out on those arising in the kidney and thyroid, and to a lesser extent salivary gland, where such neoplasms are larger and more common than in the ocular adnexa. Although there is some variation in the molecular changes in oncocytic neoplasms of different tissues, there are, as

might be expected in light of convergent differentiation, general similarities.[28] Oncocytic metaplasia and neoplasia reflect complex changes in mitochondrial metabolism and bioenergetics, as well as nuclear and mitochondrial genomics, and only a greatly simplified account can be presented in this review.

Normally mitochondria occupy up to 25% of the cytoplasmic volume and their principal function is to support aerobic respiration via the process of oxidative phosphorylation (OxPhos) and allow the generation of adenosine triphosphate (ATP) to satisfy the cell's energy requirements.[29] Four protein complexes (I–IV) incorporated within the cristae mitochondriales, the folds of the inner mitochondrial membrane, form the platform for electron transport from nicotinamide adenine dinucleotide hydrogen or succinate in the tricarboxylic acid cycle to oxygen [Table 1]. This transport is accompanied by the movement of protons from the mitochondrial matrix to the space between the inner and outer mitochondrial membranes. The electrochemical gradient thus established is then eliminated through complex V, ATP synthase, which catalyzes the phosphorylation of adenosine diphosphate to ATP.[30]
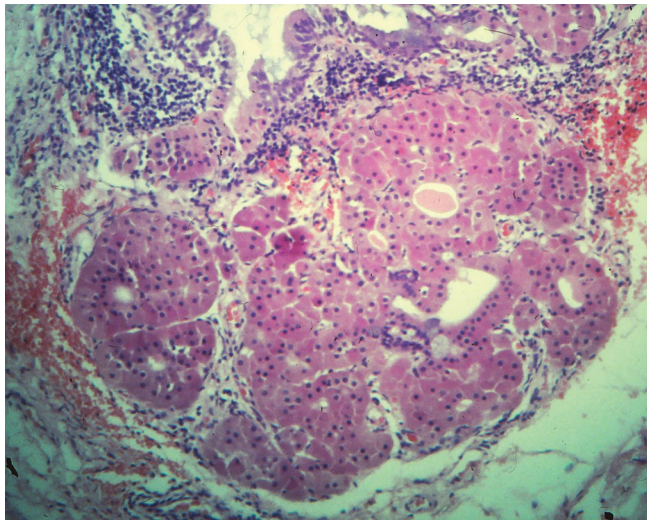

Figure 7: Biopsy of lacrimal sac mucosa from a patient with chronic dacryocystitis. In the upper part of the picture, the surface epithelium shows oncocytic metaplasia where it lines one of the crypts of the sac. In the lower part of the picture, there is a lobular proliferation of tubular structures lined by oncocytes at the base of the crypt (Hematoxylin and eosin; original magnification, ×100)

The assembly of the respiratory chain is governed by both the mitochondrial genome (mtDNA) and the nuclear genome (nDNA). The genes of mtDNA encode 13 proteins, all of which form subunits of complexes I, III, IV, and V [Table 1]. Other subunit proteins are encoded by genes in nDNA, and proper assembly of the complexes requires coordinated expression of both sets of genes. Malfunction of the mitochondria may thus potentially result from mutations in either mtDNA or nDNA.[29]

Although many solid tumors display a reduction in mitochondrial numbers and mtDNA, the opposite is true of oncocytomas, the extent of mitochondrial proliferation depending at least in part on the tissue of origin.[28] In a study of oncocytic thyroid tumors, Savagner *et al.* showed that, despite increased mtDNA and transcripts of some complex I subunits, ATP synthesis was reduced and this was attributed to an increase in UCP2, a nDNA-encoded protein that can uncouple ATP synthesis from OxPhos.[31] They suggested that mitochondrial proliferation in these tumors might be an adaptive response to the reduction in ATP synthesis. A similar conclusion was drawn by Simonnet *et al.* who noted an overall decrease in OxPhos in renal oncocytoma, despite the proliferation of mitochondria as evidenced by increased mtDNA content and citrate synthase activity (a marker for mitochondrial content of a cell).[32] Of the respiratory chain complexes, only complex IV was significantly increased and complex I was undetectable in that study. Subsequent studies confirmed a deficiency in complex I in both renal oncocytomas and oncocytic thyroid tumors.[33,34] Loss of complex I is thought to be an early event and a driver of tumor formation in renal oncocytoma, possibly through suppression of apoptosis, with subsequent loss of chromosome 1 and overexpression of cyclin D1 potentiating growth of the tumor.[35]

Why the mitochondria that accumulate in oncocytes have an abnormal morphology has yet to be fully elucidated but presumably reflects the significant metabolic stress placed on the mitochondria by the disruption of the respiratory chain. Although the increased numbers of mitochondria have long been attributed to increased biogenesis, evidence is growing that defective clearance of abnormal mitochondria by impaired autophagy may also contribute.[27] Mitochondria-eating protein is a tumor suppressor that promotes the elimination of abnormal mitochondria by autophagy (mitophagy) and its expression has been found to be decreased in oncocytic thyroid tumors.[36]

Table 1: Protein complexes of the respiratory chain

Complex	Biochemical name	Subunits derived from mtDNA	Subunit mutations in oncocytoma
I	NADH dehydrogenase	ND1, ND2, ND3, ND4, ND4L, ND5, ND6	ND1, ND4, ND5
II	Succinate dehydrogenase	None	-
III	Ubiquinol cytochrome c oxidoreductase	Cytochrome b	Cytochrome b
IV	Cytochrome c oxidase	COI, COII, COIII	COI, COII, CO3
V	ATP synthase	ATP6, ATP8	-

All complexes are assembled from translation products of genes in both mtDNA and nDNA, with the exception of Complex II, which is derived solely from nDNA. Based on Luo *et al.*[29] and Garcia-Heredia and Carnero.[30] ATP: Adenosine triphosphate, NADH: Nicotinamide adenine dinucleotide hydrogen

There has been much research into the interrelationships of the nuclear and mitochondrial genomes and mitochondrial and cellular metabolism in oncocytic neoplasms, and from this, clues have emerged as to how these tumors form and why they rarely, if ever, become malignant.[29] Complex I has been shown to be a component of apoptotic pathways and acts as a tumor suppressor; its loss will interrupt apoptosis and promote tumor growth.[33,35] The loss of complex I results from a number of loss-of-function mutations in the mtDNA [Table 1], the causes of which are not entirely clear. Reactive oxygen species, generated through the leakage of oxygen from the respiratory chain, are capable of producing mutations in mtDNA, although the presence of increased levels of the antioxidant glutathione in some oncocytomas may serve to counteract this.[30,37] The increased level of glutathione also inhibits apoptosis and malignant change.[37] Mutations in mtDNA can be homoplasmic, i.e., all copies of mtDNA within a cell are identical, or heteroplasmic, where variants with different sequences coexist within a cell. Homoplasmic mutations producing disruption of complex I have been shown to inhibit stabilization of hypoxia-inducible factor 1α. Since this factor mediates the metabolic responses that cells require to undergo malignant transformation, oncocytes with these mutations do not progress to malignancy.[38]

Mutations in nDNA genes encoding subunits of complex I have also been described in oncocytic thyroid neoplasms, but these are not common and are not thought to play a major role in tumorigenesis.[39] Disturbed mitochondrial function, however, does result in activation of p53, which acts to suppress tumor formation and malignant change.[27,29] Should mutations occur in the *TP53* gene, malignant change may follow, at least in renal oncocytoma.[27] In the only molecular genetic study of an ocular adnexal oncocytoma to date, Mikkelsen *et al.* confirmed the mutations in the *ND5* gene for complex I and also noted a gain of one copy of chromosome 8 and loss of one copy of chromosome 22.[25] Other chromosomal imbalances have been identified in renal oncocytoma, some of which may lead to malignant transformation.[27]

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Conflicts of interest
There are no conflicts of interest.

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