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Oncocytic Tumors in the Kidney: A Tri-Focal Review – Integrated Pathological, Cytopathological, and Molecular Perspectives, Part 2

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Abstract
Background: This second of two parts review is devoted to the practical aspects of fine needle aspiration biopsy diagnosis of renal oncocytoma and the interesting biology underlying the morphologic transformation of oncocytes. ***Summary:*** In the first section, we describe the most useful cytologic variables for the recognition of oncocytoma since its first cytologic description 44 years ago. The usefulness of the recently introduced cytologic diagnostic category of "low-risk oncocytic neoplasm" is discussed, as well as the known problems of differential diagnosis. The second section deals with the molecular aspects of oncocytes, with special emphasis on correlating it with the peculiar morphology of oncocytic tumors and their less aggressive behavior. First, why does this accumulation of abnormal mitochondria occur, and second, what are the consequences? Regarding oxidative phosphorylation, oncocytes show a dysfunctional respiratory complex that makes them unable to respond adequately to the hypoxia so typical of the neoplastic environment. ***Key Messages:*** The low-risk oncocytic neoplasm category is so relevant that they may limit the possibility of an accurate diagnosis in small specimens, such as FNA and core biopsies. However, this must be compatible with the possibility of making a useful diagnosis for the therapeutic management of the patient. Further, we discuss the genes and molecules responsible for mitochondrial dysfunction, and, finally, the molecular differences between sporadic oncocytomas and those associated with a hereditary context.

Introduction

The importance of specific cytological recognition of oncocytoma lies in the fact that it is a relatively common renal neoplasm with benign behavior. Most tumors are discovered incidentally, and many of these asymptomatic

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patients can benefit from conservative management (surveillance follow-up). Unfortunately, the central scar visible in imaging studies is not specific since it may be present in other slowly growing renal tumors such as eosinophilic chromophobe renal cell carcinoma (ChRCC). Therefore, the interest of cytopathologists in making a specific diagnosis has always been very high.

In the second section, the molecular aspects of oncocytes are discussed. The biology of oncocytic cells, or oncocytes, renal as well as others, has been dissected at the genetics, molecular biology and biochemical level with the aim to unravel the mechanisms that lead to such a unique phenotype. The rather paradoxical entity that is an oncocyte has, in fact, represented a mystery in cell biology for a long time: how can a population of cells whose cytoplasm is entirely packed with mitochondria originate or constitute a proliferating cancer mass has been long debated. The conundrum was exacerbated with the discovery that mitochondria within oncocytes are dysfunctional, and energy production via respiration is hampered. Although this was precisely what Warburg [1] predicted at the beginning of last century to engender cancer and explain the favored glycolytic metabolism of tumor cells, it has become increasingly clear that cancer cells need a functional mitochondrial respiration to thrive and progress to malignancy, de facto confuting the equation that a damaged oxidative phosphorylation equals cell transformation and onset of aggressive potential.

Cytopathological Features of Renal Oncocytoma and Its Differential Diagnosis

Background

Cytological characterization of renal oncocytoma began shortly after its first histopathological description in 1976 [2]. During the course of >40 years, we have learned a lot about its cytopathologic features and, likewise, about the difficulties of a precise diagnosis in fine needle aspiration biopsy (FNAB) or core needle biopsies [3–11].

Cytopathologic and Immunocytochemical Features

The main cytopathologic and immunocytochemical features include [3–11] the following:

- Smears are moderate to hypercellular and consist of small cellular groups and dispersed single cells (Fig. 1). Sometimes larger tissue fragments containing thin vessels are present. The background is clean with no necrosis or macrophages.
- Cells are round to polygonal and usually show well-defined contours. Variation in cell size is not a remarkable finding so even at low power magnification, it has a rather monomorphic appearance (Fig. 1). The nucleus tends to occupy a central position. No plasmacytoid, rhabdoid, or spindle-shaped cells are present.
- The most relevant morphologic finding is the cytoplasm, which is abundant, deeply stained, granular with no significant perinuclear clearing or vacuolization (Fig. 1). This peculiar cytoplasm raises immediately the possibility of oncocytoma and its differentials. There are no clear cells.
- The nuclei are round with no irregularities of its membrane. Binucleation is common. Chromatin is finely granular and one small nucleolus is often seen (Fig. 1). No mitotic activity or apoptosis is seen.
- "Oncoblasts" and degenerative nuclear atypia are two uncommon findings that may look worrisome but lack clinical significance. The term "oncoblasts" is used for a subset of tumoral cells that have scarce cytoplasm and therefore a high N:C ratio (Fig. 2). Occasional cells may show degenerative nuclear atypia (Fig. 2), resembling that seen in endocrine tumors or schwannoma. It is a focal finding and associates no mitoses or apoptotic figures.
- Nested and tubular architectural arrangement are a very characteristic and helpful diagnostic feature that can be easily evaluated in a cell block.
- Regarding immunocytochemistry the combination CD117+/CK7– is very useful for diagnosis. Tumor cells consistently express CD117 (membranous and cytoplasmic) (Fig. 1), while CK7 is mostly negative with scattered positive cells. Vimentin, carbonic anhydrase IX, AMACR, and the colloidal iron histochemical reaction are typically negative.

Differential Diagnosis

In summary, the relatively monotonous appearance and large, dense, well-defined cytoplasm, which reflects the packing of mitochondria, are noteworthy findings. The main diagnostic problem in cytologic specimens or small biopsies lies in the morphological heterogeneity shown by many renal tumors, especially large ones. This is an intrinsic and unavoidable limitation of small samples that should be reflected in the diagnostic report. Due to its frequency in clinical practice, there are three main differential diagnoses include normal kidney, clear cell RCC rich in eosinophilic cells, and eosinophilic variant ChRCC. The normal kidney is easily identifiable in a biopsy but can be misleading in fine needle aspiration

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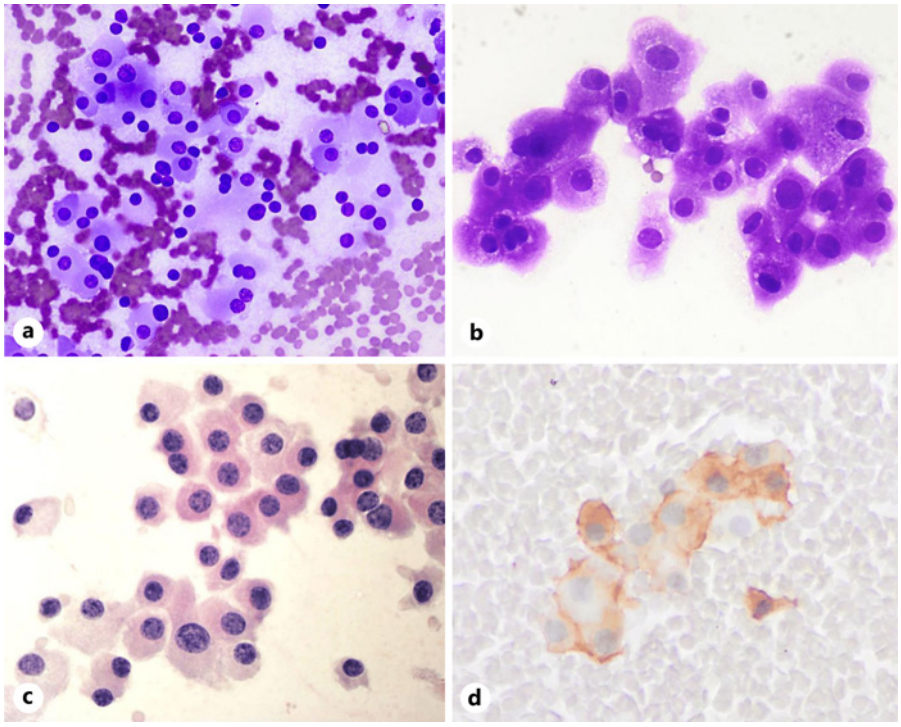

Fig. 1. a Numerous loosely cohesive cells showing abundant deeply stained cytoplasm. Nuclei are round and show minimal to moderate pleomorphism (Diff-Quik. ×200). **b**, **c** At higher magnification, cells are polygonal with abundant granular cytoplasm and well-defined cellular limits. The nuclear contour is smooth with no indentations and chromatin is regularly distributed (Diff-Quik and Papanicolaou. ×400). **d** Immunocytochemical expression of CD117.

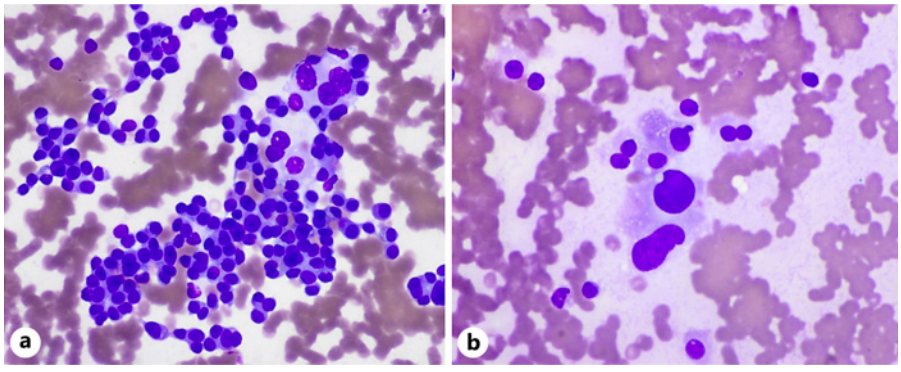

Fig. 2. Uncommon features in oncocytoma. **a** As opposed to usual oncocytic tumoral cells, "oncoblasts" have a reduced amount of cytoplasm and subsequently a high nuclear to cytoplasmic ratio (Diff-Quik. ×400). **b** Occasional cells showing large, degenerative-appearing nuclear pleomorphism are not a rare finding in oncocytoma. When present, this is a focal finding (Diff-Quik. ×600).

biopsy (FNAB) samples [12, 13]. Proximal tubular cells, which constitute most of the cortex, show a dense granular cytoplasm that mimics that of oncocytoma (Fig. 3). In addition, they can express CD117. Clues for their recognition are main distribution on cohesive fragments with few single cells, ill-defined plasma membranes (syncytial-like groups) (Fig. 3), cytoplasmic lipofuscin, and accompanying collecting tubular clusters and glomeruli [13]. Clear cell RCC rich in eosinophilic cells may rarely resemble oncocytoma. Fortunately, most cases will show diffuse nuclear atypia, prominent nucleolus, and cellular pleomorphism. The eosinophilic variant of ChRCC is the main differential diagnosis since it may lack significant atypia and expresses CD117. As opposed to oncocytoma, chromophobe RCC will show relevant cellular polymorphism with round to polygonal cells that show great variation in size (Fig. 3). Another characteristic features are the indented nuclear contour ("wrinkled" nuclei), and intense expression of CK7 [14, 15]. In addition, there is now a long list of neoplasms which, without being oncocytomas, may have an obvious oncocytic morphology.

Low-Risk Oncocytic Neoplasm and Its Diagnostic Criteria

The aim of both FNAB and core needle biopsies is a diagnosis of certainty, but surgical pathologists and cytopathologists are aware that this is often not possible.

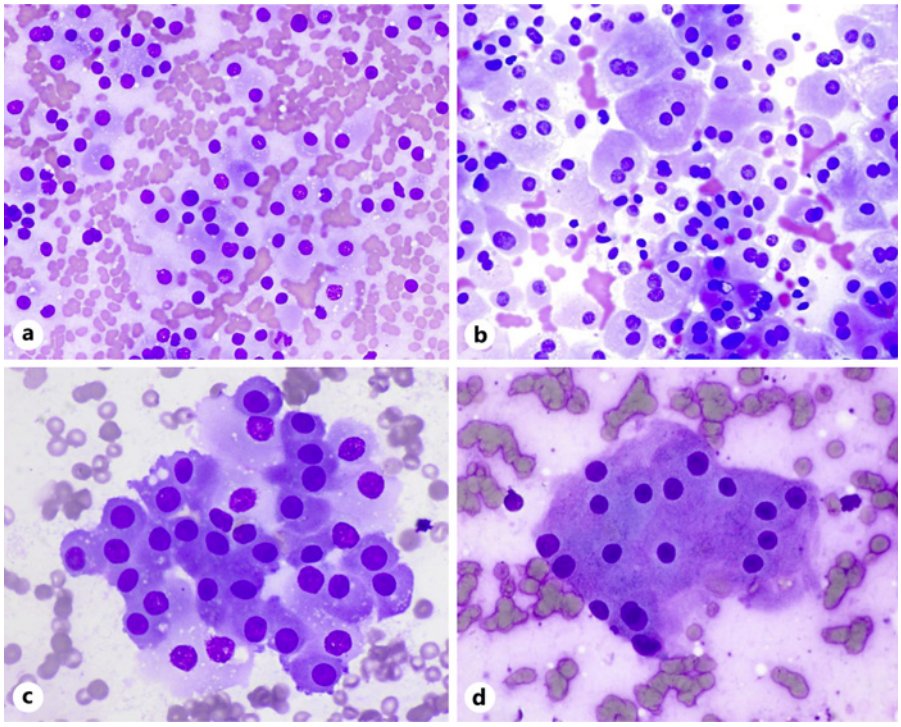

Fig. 3. Oncocytoma (**a**, **c**) and main differentials (**b**, **d**). **a** Oncocytoma showing discohesive uniform cells with deeply stained cytoplasm (Diff-Quik. ×200). **b** In eosinophilic variant of ChRCC, the cell pattern distribution and quality of the cytoplasm is similar, but cell size variation is prominent with large, intermediate and small cells as opposed to oncocytoma (Diff-Quik. ×200). **c** A cellular fragment of an oncocytoma showing relatively well-defined cellular limits (Diff-Quik. ×400). **d** Normal renal cells from the proximal tubule have abundant deeply stained, granular cytoplasm. Cell limits are ill-defined creating a syncytial image (Diff-Quik. ×200).

The diagnostic criteria for oncocytoma or ChRCC must be kept strict, and a different diagnosis should be used for "gray zone cases." The term "oncocytic neoplasm of low malignant potential, not further classified" was recently proposed by the Genitourinary Pathology Society (GUPS) to designate tumors demonstrating borderline and equivocal features between oncocytoma and ChRCC [16]. Similarly, a group of expert renal cytopathologists has recently proposed using the term "low-risk oncocytic neoplasm" for FNAB samples [17]. Diagnostic criteria for this diagnostic category include the following: loosely cohesive clusters of oncocytic tumoral cells, no nuclear atypia ("wrinkled" nuclei of chromophobe RCC), no macronucleoli, nested architectural arrangement (on cell block), and strong CD117 expression. These criteria are designed to exclude cases of papillary RCC with eosinophilic cytoplasm, clear cell RCC with oncocytic features, translocation associated RCCs, eosinophilic solid and cystic (ESC) RCC, and fumarate hydratase-deficient RCC. When strictly applied these criteria will select under the "low-risk oncocytic neoplasm" category cases of oncocytoma, eosinophilic ChRCC and the hybrid oncocytic tumors of Birt-Hogg-Dubé syndrome. From a practical perspective, it is a useful diagnostic category that groups cases with a low risk of malignancy. Using a 5-year survival rate of 78%–100% for ChRCC, the 5-year survival rate for this diagnostic category would be 95%–100% and the estimated risk of malignancy 21% [17, 18]. Other oncocytic tumors such us low-grade oncocytic tumor and eosinophilic vacuolated tumor (EVT) have only recently been described and there are not enough cytologic descriptions. Given the enormous similarities that they have with oncocytoma, it is quite possible that some of the old cases of oncocytoma now correspond to one of these entities. Fortunately, they are low-grade neoplasms with a benign behavior [19].

Molecular Perspectives on Renal Oncocytomas

Background

The commonest genetic feature to oncocytes, whether they arise in endocrine or non-endocrine organs, is damaging mutations in the mitochondrial DNA (mtDNA), particularly in respiratory complex I (CI) genes [20–23]. They explain the dysfunctional oxidative phosphorylation and support the hypothesis of a retrograde signal from the mitochondria to the nucleus that triggers organelle biogenesis in the attempt to compensate for the decrease in energy production, ultimately leading to mitochondrial hyperplasia. Such mechanism appears to be mediated by the Peroxisome Proliferator Activated Receptor gamma Coactivator 1a (PGC1a), which has been found overexpressed in

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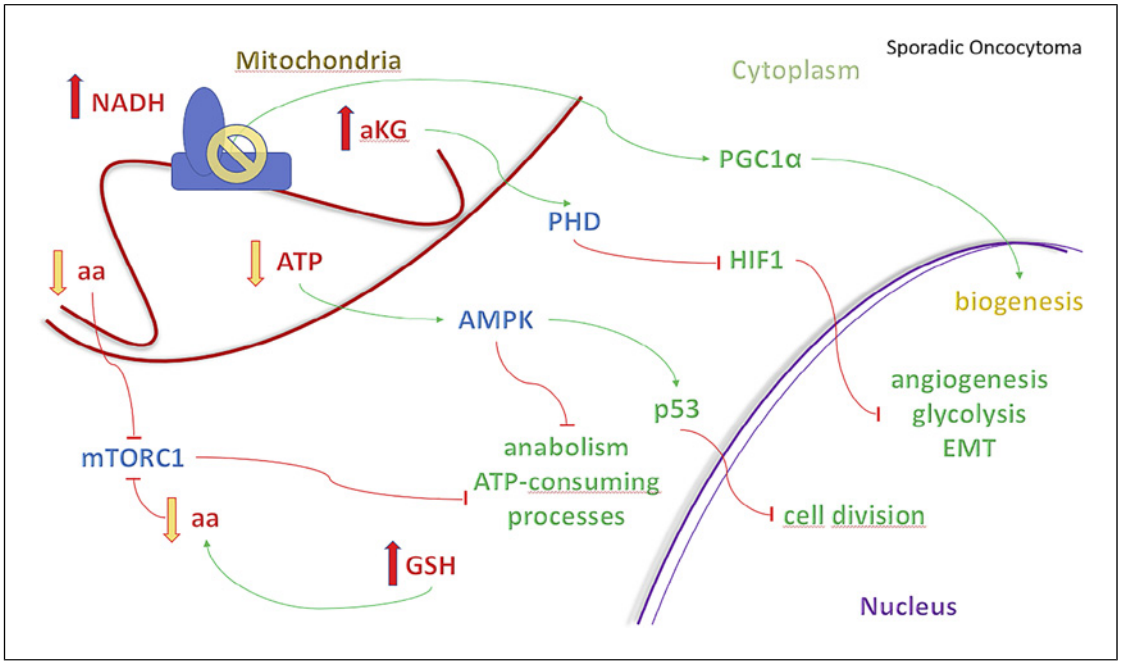

Fig. 4. Schematic representation of the main molecular players in sporadic oncocytoma. Complex I deficiency results in a variety of effects, such as (from top to bottom): (1) boosting of PGC1α expression in order to promote mitochondrial biogenesis; (2) HIF1 destabilization/inhibition through the increase in a-KG-dependent PHD activity, which in turn prevents angiogenesis, glycolysis, and EMT; (3) mitochondrial energy production impairment showed by a reduction in ATP level generation which may enhance the AMPK-p53 axis, hindering cell division; (4) amino acid deficiency that leads to mTORC1 inhibition impairing anabolic processes.

oncocytic cells [24, 25], and shown to increase upon CI damage [26]. Interestingly, mutant BRAF (V600E) was shown to decrease PGC1a expression and down-modulate mitochondrial respiration [27]. As this oncogene is found mutated at high frequency in subsets of oncocytic tumors, such as the tall-cell variant of papillary thyroid cancer [28], it is plausible that it may predispose to mtDNA mutations occurrence by relieving selective pressures that normally act when a functional respiratory chain is required. Nonetheless, the accumulation of disruptive mtDNA mutations, which are normally purified in most human neoplasms [29], exquisitely occurring in oncocytomas [30], may be the consequence of a disruption in the mitophagic process due to a defect in Parkin, the protein that presides to such function [31]. The lack of clearance of damaged organelles would hence allow them to persist, explaining their deranged morphology. Interestingly, overexpression of mitochondrial dynamics fission factor Drp1 has been described in thyroid oncocytic cells [32]. As fission ought to be carried out before mitochondria are recycled through mitophagy/autophagy, it is plausible that organellar degradation is short-circuited at this stage, leaving a fragmented network composed of smaller, fixated mitochondria, a phenotype that has also been observed when CI damage is induced by mtDNA mutations [33]. It is not surprising, therefore, that a deletion of autophagy regulator ATG7 is able to trigger oncocytic transformation in lung carcinoma, with a concomitant dampening of aggressive and metastatic behavior [34]. Overall, although it is nowadays accepted that disruptive mtDNA mutations are secondary event to initial transformation in oncocytic tumors, the question remains open as to whether they occur prior or consequent to mitochondrial hyperplasia (Fig. 4).

The most dramatic implication of oncocytic change for a cancer cell is likely its incapacity to respond to hypoxia, which derives directly from CI derangement. Indeed, accumulation of CI substrate, i.e., NADH, which follows the complex dysfunction, leads to the allosteric inhibition of the Krebs cycle enzyme a-ketoglutarate (a-KG) dehydrogenase. In turn, the subsequent accumulation of the latter enzyme's substrate, a-KG, fosters the reaction of the prolyl hydroxylase responsible for the continuous degradation of hypoxia-inducible factor 1a (HIF1a), whose stability is needed to respond to hypoxia [35, 36]. Overall,

therefore, HIF1a in oncocytes is kept under constant degradation even during the oxygen deprivation period that every tumor mass faces while growing. This is nowadays considered the main barrier to overt malignancy that is ascribed to oncocytomas, which may be overcome during cancer progression if mtDNA mutations are purified and CI function recovered. This scenario may explain the close association between severely pathogenic mtDNA mutations, along with their induced metabolic phenotype, which are typical of benign oncocytomas, and their indolent behavior, as previously suggested [21, 23]. In this context, although proven in cell models where oncocytic change has been induced artificially, it is interesting that the inability to respond to hypoxia forces cancer cells to depend on non-cell autonomous mechanisms for vascularization, and hence to rely on the stromal component [35]. Indeed, the production of vascular endothelial growth factor (VEGF) from oncocytes is expected to be curbed, as *VEGF* is a transcriptional target of HIF1a. Whether this occurs in human oncocytic tumors is yet to be determined, as no current studies have focused on dissecting the type of angiogenesis or the tumor microenvironment components that surround oncocytic cells.

Overall, oncocytes appear to be energetically impaired and oncocytic tumors generally less aggressive than their non-oncocytic counterpart, likely because of metabolic constraints as a consequence of a severe mitochondrial damage. Indeed, lack of CI renders cells unable to synthesize crucial amino acids such as Aspartate [37] and Aspartate-derived Asparagine, causing a slow-down in the anabolism of proteins mediated by nutrient sensor mTORC1 [38]. At the same time, amino acids such as those involved in the gamma-glutamyl cycle appear to be diverted to an aberrant synthesis of antioxidant glutathione, likely to buffer the high levels of oxidative stress that follows the accumulation of dysfunctional mitochondria, as it has been shown to occur in renal oncocytoma [39]. This loop is further amplified by the phosphorylation of energy stress sensor AMPK, which is activated when ATP levels drop with the aim to shut down anabolism. It is worth mentioning that under energetic stress, AMPK is capable of activating tumor suppressor p53 to trigger growth arrest [40]; the very low frequency of *TP53* mutations in oncocytic tumors [41] suggests that the relatively low mitotic index of oncocytic tumors harboring mtDNA mutations may be due to the presence of a functional p53 activated by AMPK. These mechanisms have been shown in vitro to accompany oncocytic transformation, providing an explanation for indolence, and setting the basis to understand why energy-requiring cellular processes, such as iodide uptake in thyroid cells [42], may not easily be carried out by oncocytes.

Renal Oncocytomas in the Context of Hereditary Syndromes

Renal oncocytomas have been described in genetic hereditary syndromes encompassing Birt-Hogg Dubé (BHD), Tuberous sclerosis complex (TSC) and pheochromocytoma/paraganglioma syndromes [43]. Such oncocytic lesions represent a challenging paradigm, even if they are not a major diagnostic criterion of these genetic conditions [44–46].

BHD is an autosomal dominant disease, caused by loss-of-function (LOF) variants in the *FLCN* gene, that predisposes patients to develop fibrofolliculoma, lung cysts and bilateral multifocal renal tumors with different histologies, including oncocytoma in 5% of cases. Interestingly, nearly half of patients show renal oncocytosis in the normal kidney parenchyma surrounding the tumors [47]. *FLCN* acts as a typical tumor suppressor gene in BHD patients, whose germline variants are insertions, deletions, nonsense and splice-site variants and in whom somatic variants in the second copy of *FLCN* or loss of heterozygosity (LOH) at the same locus were observed in tested kidney lesions, resulting in the lack of FLCN functional protein. On the contrary *FLCN* loss is not a common driver in sporadic oncocytomas [48–51].

TSC is a neurocutaneous condition involving abnormalities of the skin (hypomelanotic macules, facial angiofibromas, shagreen patches, ungual fibromas), brain (subependymal nodules, cortical tubers, and subependymal giant cell astrocytomas), heart (rhabdomyomas), lungs (lymphangioleiomyomatosis), and kidney (benign renal angiomyolipomas, epithelial cysts, oncocytoma, renal cell carcinoma). Oncocytomas are not the most striking sign in these patients but occur more frequently than the general population and commonly display a benign course [52, 53]. TSC is caused by heterozygous pathogenic variants in *TSC1/TSC2* tumor suppressor genes, which fit the Knudson two-hit hypothesis with one germline inactivating allele affecting hamartin or tuberin respectively and a somatic mutation or loss of heterozygosity in the second one as observed in renal and pulmonary lesions [54, 55].

Hereditary paraganglioma-pheochromocytoma syndromes are mainly characterized by paragangliomas and

pheochromocytomas, neuroendocrine tumors arising from sympathetic tissue in the adrenal gland or from neural crest progenitors located outside of the adrenal gland. However, mutations in genes encoding succinate dehydrogenase complex subunit B/C/D proteins (SDHB/C/D), which participates in both the Krebs cycle, fostering the direct and reverse conversion of succinate to fumarate, and as mitochondrial respiratory chain complex II, have been also associated with an increased risk of renal tumors including oncocytomas [43, 56]. A singular case of renal oncocytoma has been reported in the context of the Von Hippel-Lindau (VHL) syndrome [57].

The reconstruction of the molecular pathways differently or commonly activated or repressed in such syndromic cases is of help in the comprehension of the metabolic reprogramming that may lead, or be related to, the genesis of the oncocytic phenotype in renal lesions.

Molecular Players Underlying Metabolic Rewiring in Renal Oncocytoma: Differences and Similarities between Sporadic and Syndrome-Related

mTOR Complex I

It is worth noting that BHD and TSC clinical signs strongly reflect mTOR hyperactivation. Folliculin, whose function is lost in BHD following *FLCN* LOF variants, plays a key role in the regulation of the mTORC1 pathway. Physiologically, FLCN can promote or hinder mTORC1 activation according to nutrient and energy availability [58–60]. This occurs through the interaction with two different binding proteins, folliculin-interacting protein 1 and 2 (FNIP1 and FNIP2), forming an energy sensor complex that binds and activates the c subunit of AMPK, ultimately and negatively regulating mTOR activity [58]. Therefore, the loss of FLCN that occurs in BHD disease results in mTORC1 and mTORC2 activation, promoting cell proliferation [61]. Controversially, however, Yan et al. [62] reported chronic AMPK activation in FLCN-deficient mouse embryonic fibroblasts. Hamartin and tuberin, encoded by *TSC1* and *TSC2*, function as a heterotrimeric complex (along with TBC1D7) with the role of a GTPase-activating protein (GAP) which maintains the small GTPase RHEB in its GDP-bound form, unable to activate mTORC1 [63]. Thus, the TSC complex normally acts to restrain mTORC1 under conditions that are adverse for proliferation, such as when growth factors are absent or when oxygen is scarce [64]. In TSC patients, therefore, the mTORC1 pathway is deemed to be constitutively active [65], similarly to FLCN-null BHD-associated tumors. This is bound to occur also in tumors with a similar histomorphology of EVTs, a subgroup of oncocytoma-like tumors, reported in the context of TSC [66]. It is likely not coincidental that sporadic EVTs have been shown to harbor nonoverlapping activating mutations in *MTOR* and inactivating variants in *TSC2* or *TSC1*, suggesting that the same molecular mechanisms involving mTORC1 hyperactivation underlie cell transformation in both syndromic and sporadic EVT forms [67]. Overall, BHD- and TSC-associated oncocytomas share mTORC1 hyperactivation as a distinctive hallmark. To our knowledge, no evidence exists on mTOR pathway regulation in SDH syndrome, although in a mouse model of SDH knock-out β-cells, a hyperactivation of mTORC1-regulated anabolism has been observed, which was partially reverted by rapamycin treatment [68].

With respect to cytogenetic abnormalities, they are typical of sporadic oncocytomas but not of hereditary forms such as BHD tumors [69]. Indeed, unbalanced chromosomal rearrangements have been frequently described in sporadic oncocytomas, involving chromosome 1 loss, which contains mTOR [70], thus highlighting the lack of mTOR pathway upregulation in sporadic tumors at variance with the hereditary mTORC1 hyperactivation.

PGC1α: Where Phenotypes Converge

While they are not recurrent in syndromic oncocytomas [71], mtDNA disruptive mutations are frequently born by sporadic renal oncocytic tumors. Such mutations were identified in complex I genes, but also in cytochrome b, in cytochrome c oxidase subunits, complex V, and the D loop [20, 21]. In these tumors, similarly to other oncocytomas harboring the same type of mtDNA mutations, the consequences of OXPHOS deficiency have been characterized. Proteome surveys identified a general increase in mitochondrial proteins expression, except for CI subunits, which is expected in the presence of a CI mtDNA lesion. In particular, proteomics data have shown in renal oncocytomas a 2.2-fold increase of proteins localized to mitochondria [39]. Furthermore, whole exome sequencing detected a 1.8-fold increase of mtDNA reads in sporadic renal oncocytomas compared to healthy kidneys [39]. These findings are consistent with the growing knowledge that PGC1α may underlie such mitochondrial biogenesis induction as in other sporadic oncocytomas [24], though the specific involvement of PGC1α has not been proven yet. This scenario implies the inability of cells to synthesize crucial amino

acids [39] and AMPK activation following unbalanced AMP/ATP ratio, which might be expected to result in mTORC1 inhibition [72], at variance with syndromic renal oncocytomas despite morphological analogies. Chronic AMPK activation leads to upregulation of PGC1α, a known target of AMPK, which in turn increases mitochondrial content and the oxidative phosphorylation rate, resulting in an augmented ROS production rate [62, 73]. Such ROS abundance was shown to boost HIF-1α transcriptional activity, leading to enhanced glucose uptake and glycolytic rate, reinforcing the Warburg effect [73]. Notwithstanding this, mitochondrial hyperplasia may be driven, in both sporadic and syndromic renal oncocytomas, by PGC1α hyperactivation via different mechanisms. Both in *FLCN*-depleted cells and in *TSC1*-deleted mice, this occurs through a boost in mTORC1 pathway activity [74, 75]. Alternatively, somewhat, PGC1α may be also stimulated by AMPK activation, as reported by Yan et al. [62]. In sporadic cases, on the other hand, PGC1a hyperactivation would depend on the retrograde signaling triggered by mtDNA mutations-induced OXPHOS dysfunction [22].

HIF-1α

A major player whose regulatory asset appears to differ between sporadic and syndromic renal oncocytomas is HIF-1α. In TSC, besides PGC1α, mTORC1 activation also induces HIF-1α and angiogenesis, thereby coupling cell growth with an increase in oxygen and nutrient delivery [43]. In addition, in SDH and VHL syndromes, HIF-1α has been found to be a common target for metabolic reprogramming in renal cancer cells and its stability increased by either a VHL protein deficit or succinate dehydrogenase deficiency as a consequence of the succinate and fumarate oncometabolites accumulation, which has an inhibitory effect on the prolyl hydroxylase-VHL axis [56, 76]. Therefore, HIF-1α may play a crucial role in the survival and adaptation of syndromic oncocytomas, sustaining cells proliferation through nutrient supply following angiogenesis promotion. However, contrarily, HIF1-α stabilization levels are dramatically impaired in sporadic renal oncocytomas since complex I mtDNA disruptive mutations associate with a condition of pseudonormoxia [73]. This has relevant consequences on the metabolic reprogramming occurring in oncocytes. Interestingly, sporadic renal oncocytomas do not rely upon their glycolytic capacity to sustain metabolism when OXPHOS is compromised, which was postulated in other oncocytomas, and they may not display a HIF1-dependent proglycolytic signature [36]. Indeed, alpha-enolase and pyruvate carboxylase were shown to be decreased in renal oncocytomas when compared to normal kidney tissues, and both pentose phosphate pathway and glucose production from lactate were downregulated [39]. Moreover, reductive carboxylation of glutamine, which has been shown to be the metabolic adaptive route of cells with disrupted mitochondrial respiration [77, 78], may not play a major role as energy source since a 25-fold decline in cytosolic isocitrate dehydrogenase was found in renal oncocytomas [39]. Overall, in sporadic oncocytomas, HIF-1α destabilization curbs the glycolytic capacity, resulting in a non-proficient Warburg effect and in a more general metabolic blockade, since these tumors cannot rely on mitochondrial respiration or reductive carboxylation of glutamine. In contrast, HIF-1α activity found in hereditary syndromes might boost a glycolytic response in oncocytomas, possibly sustaining cells proliferation; nevertheless, despite all these clues, no conclusive evidence has been reported to date on the metabolic rewiring of syndromic oncocytomas.

Syndromic and Sporadic Renal Oncocytomas: Morphological Phenocopies with Distinct Molecular Patterns?

In brief, renal oncocytomas show different features in sporadic cases compared to hereditary syndromes (Fig. 5). In the first setting, CI impairment is the main molecular hallmark, while in hereditary oncocytoma, mtDNA mutations are not recurrent. Indeed, BHD, TSC and SDH syndromes defining features depend on a loss of function of negative regulators of the mTOR pathway and display an array of signs with variable severity, of which oncocytomas can be a component even if they are not a major diagnostic criterion. However, other factors might be required to affect the disequilibrium towards a more benign phenotype like oncocytoma, in analogy with the case described by De Luise et al. [57] in a VHL syndrome patient harboring not only a LOF mutation in *VHL* but also in *MT-CO1*, a rare finding reminiscent of more typical sporadic tumors features. Moreover, further studies are needed to improve the understanding of how the hyperactivation of mTOR pathway caused by the syndrome is modulated in order to drive the development of oncocytomas, which share the same histological features of the sporadic lesions, even if apparently molecularly divergent. Indeed, while syndromic oncocytomas present mTORC1 activation and HIF-1α stabilization, the sporadic counterpart is characterized by mTORC1

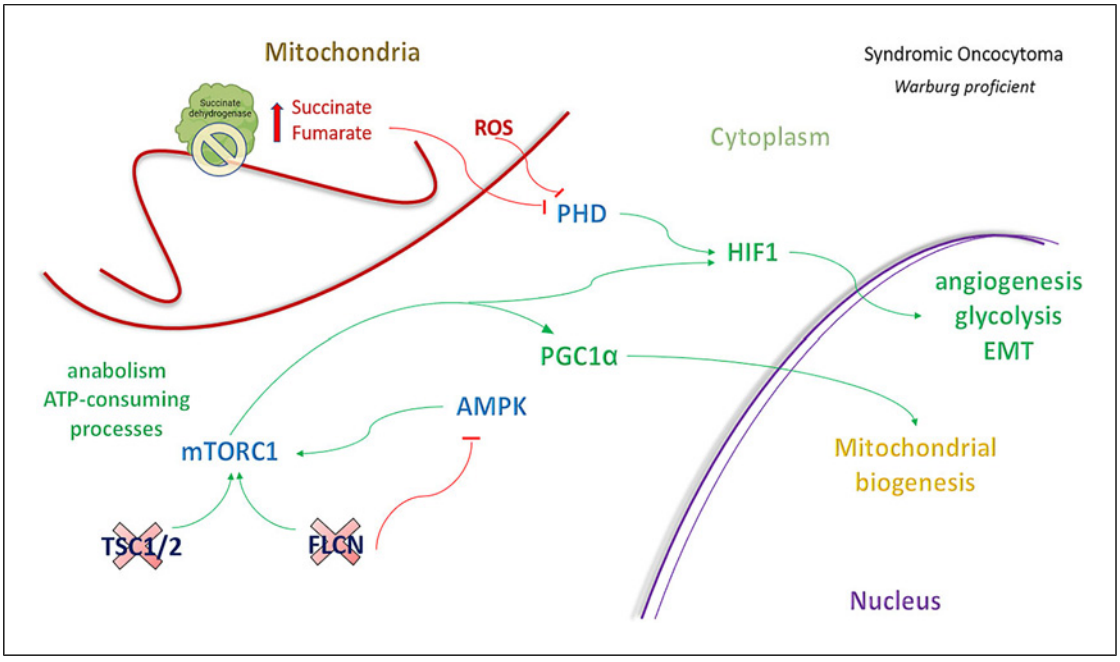

Fig. 5. Schematic representation of the main molecular players in syndromic oncocytoma. Hereditary syndromes may affect oncocytoma metabolism in different ways depending on their genetic background. From top to bottom, on one hand, angiogenesis, glycolysis, and EMT are promoted through HIF1 stabilization either through PHD inhibition resulting from Succinate dehydrogenase deficiency and ROS accumulation or through mTORC1 activation driven by TSC1/2 or FLCN deficiency. On the other hand, FLCN and TSC1/2 loss of function could also enhance anabolic processes and PGC1α-driven mitochondrial biogenesis via mTORC1 activity promotion.

inhibition and HIF-1α destabilization; however, both seem to converge on PGC1α-driven mitochondrial biogenesis. The apparent inconsistency, in syndromic oncocytomas, of the co-existence of HIF-1α stabilization and mitochondrial biogenesis induction might be clarified by the fact that HIF-1α is known to have an inhibitory effect on PGC1β [79], while PGC1α is boosted by the constitutive activation of mTOR pathway. Paradoxically, such condition could promote a loop in favor of PGC1α activity, which would explain the increased mitochondria amount in syndromic oncocytic cells, albeit this remains thus far a mere speculation warranting investigation.

Conclusion

Sporadic and hereditary oncocytomas represent an interesting paradigm of study, since dissecting their hallmark metabolic/molecular features, which enhance their benign behavior in terms of low-proliferative rate and absence of metastasis, can be translated to downgrade other malignant neoplasia. Indeed, the greatest comprehension of oncocytoma metabolism could drive the development of new therapies targeting the biological pathways in aggressive tumors [34, 80].

Conflict of Interest Statement

The authors report no conflicts of interest.

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Author Contributions

Laura Lanteri: writing – original draft; Elena Luppi: writing – original draft; Alessia Cimadamore: writing – review and editing; Gladell P. Paner: conceptualization, project administration, and writing – review and editing; José A. Jiménez Heffernan: conceptualization, writing – original draft, writing – review and editing, and visualization; and Giuseppe Gasparre: conceptualization, writing – original draft, writing – review and editing, and visualization.

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