Cathepsin K

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Cathepsin K is a papain-like cysteine protease with high matrix-degrading activity. Among several cathepsins, cathepsin K is the most potent mammalian collagenase, mainly expressed by osteoclasts. This review summarizes most of the recent findings of cathepsin K expression, highlighting its role in renal tumors for diagnostic purposes and as a potential molecular target. Indeed, cathepsin K is a recognized diagnostic tool for the identification of TFE3/TFEB-rearranged renal cell carcinoma, TFEB-amplified renal cell carcinoma, and pure epithelioid PEComa/epithelioid angiomyolipoma. More recently, its expression has been observed in a subgroup of eosinophilic renal neoplasms molecularly characterized by TSC/mTOR gene mutations. Interestingly, both TSC mutations or TFE3 rearrangement have been reported in pure epithelioid PEComa/epithelioid angiomyolipoma. Cathepsin K seems to be a downstream marker of TFE3/TFEB rearrangement, TFEB amplification, and mTOR pathway activation. Given the established role of mTOR inhibitors as a pharmacological option in renal cancers, cathepsin K could be of use as a predictive marker of therapy response and as a potential target. In the future, uropathologists may implement the use of cathepsin K to establish a diagnosis among renal tumors with clear cells, papillary architecture, and oncocytic features.

Keywords: cathepsin K ; renal cancers ; PEComa ; translocation renal cell carcinoma ; differential diagnosis ; predictive markers ; TSC1/TSC2 ; mTOR pathway ; angiomyolipoma

1. Introduction

Cathepsin K belongs to the papain-like cysteine peptidase family. It is a member of lysosomal cysteine protease, with the main function of mediating bone resorption under normal and pathological conditions. Cathepsin K is encoded by a *CTSK* gene located on chromosome 1q21.3, with eight exons and seven introns, and a similar organization of cathepsin L and cathepsin S. Mutations on the *CTSK* gene lead to pycnodysostosis, an autosomal recessive disease characterized by osteosclerosis with increased bone fragility, dysmorphic facial features, and short stature [1]. From the structural aspect, cathepsin k is a protein composed of 329-aminoacid comprising of an N-terminal signal sequence (15-amino-acid long), a propeptide (99-amino-acid long), and a catalytic unit (215-amino-acid long). The active site of cathepsin K is at the top of the molecule and contains the catalytic dyad cysteine–histidine [2].

Cathepsin K degrades collagens at different sites in the N-terminus region, and has recently been named the most potent mammalian collagenolytic endopeptidase [3]. It is mainly secreted by activated osteoclasts to degrade collagen and other matrix proteins during bone resorption, but also in the hematopoietic stem cells mobilization from the endosteal niche [4]. Because of its activity in bone resorption, it has become an important target for the treatment of osteoporosis (bone resorption exceeds bone formation), even though there is no approved drug so far [4][5]. The activity of cathepsin K is modulated by several factors: RANKL, NFAT, and microphthalmia transcription factor (MiTF) enhance cathepsin K expression, and therefore osteoclast formation and bone resorption. On the other hand, interferon (IFN)-gamma, estradiol, calcitonin, and calcium reduce it [6].

Beyond the bone, cathepsin K plays a crucial role in the central nervous, respiratory, and cardiovascular systems [7]. It is detected in neurons, as well as in glial cells, in the bronchial and alveolar epithelial cells, and in the alveolar macrophages in the normal lung, and a small amount of cathepsin K is expressed in the normal heart. Its physiological role in cellular protein turnover, collagen degradation, and remodeling of the extracellular matrix may explain the important role of cathepsin K in neurological disorders, cardiac dysfunction, and pulmonary fibrosis [8] (Table 1). It is also expressed in multinucleated giant cells, Langhans cells, and skin fibroblasts, which play an important role in the homeostasis of the dermal extracellular matrix during wound healing [9]. Taken together, the variety of processes in which cathepsin K is involved and the several diseases genetically or epigenetically associated with cathepsin K expression in either mesenchymal or epithelial tissues explain the increasing interest of scientists in this molecule.

Table 1. Cathepsin K in human diseases (except kidney).

Histotype	Morphological Features	Molecular Alteration	Cathepsin K	HMB45/Melan-A	PAX8	CD68(PG-M1)
TFE3-rearranged RCC	clear cells in nests	*ASPCR1-TFE3* fusion	negative	variable	positive	negative
	papillary architecture	*PRCC-TFE3* fusion	positive	variable	positive	negative
	variable	*SFPQ-TFE3* fusion	variable	variable	positive	negative
TFEB-rearranged RCC	biphasic appearance	*MALAT1-TFEB* fusion	positive	positive	positive	negative
TFEB-amplified RCC	high grade	*TFEB* amplification	positive	positive	positive	negative
PEComa	epithelioid cells	*TSC2* mutation	positive	positive	negative	positive
	epithelioid cells	*SFPQ-TFE3* fusion	positive	positive	negative	positive
ESC-RCC	eosinophilic solid and cystic	*TSC1/TSC2* mutation	positive	negative	positive	n.a.
EVT	high grade oncocytic	*TSC2/mTOR* mutation	positive	negative	positive	n.a.

RCC: renal cell carcinoma; ESC: eosinophilic solid and cystic; EVT: eosinophilic vacuolated tumor; n.a.: not available.

2. Cathepsin K in the Differential Diagnosis

Cathepsin K is a valuable marker in the differential diagnosis of renal cell carcinoma (Table 2). Its usefulness has been widely recognized, being included, together with a handful of immunohistochemical markers, in best practice recommendations in immunohistochemical panels to classify primary renal neoplasm [10][11].

Table 2. Cathepsin k in differential diagnosis among renal tumors.

Pattern	Histotype	Cathepsin K
clear cell	clear cell RCC	negative
	clear cell papillary RCC	negative
	chromophobe RCC	negative
	TFE3-rearranged RCC	variable
	TFEB-rearranged RCC	positive
	PEComa	positive
papillary architecture	papillary RCC	negative
	clear cell papillary RCC	negative
	TFE3-rearranged RCC	variable
	TFEB-rearranged RCC	positive
oncocytic cells	oncocytoma	negative
	chromophobe RCC	negative
	TFE3-rearranged RCC	variable
	TFEB-rearranged RCC	positive
	PEComa	positive
	ESC-RCC	positive

Pattern	Histotype	Cathepsin K
	eosinophilic vacuolated tumor	positive

RCC—renal cell carcinoma; ESC—eosinophilic solid and cystic.

Among the renal cell carcinomas with clear cells and a papillary architecture, cathepsin K is the most reliable immunohistochemical tool to discern translocation renal cell carcinoma from the most common clear cell renal cell carcinomas and papillary renal cell carcinomas, which are consistently negative for this marker [12][13]. Meaningfully, as above mentioned, immunolabeling for cathepsin K is observed in approximately half of TFE3-rearranged renal cell carcinomas, the neoplasm most confused with clear cell renal cell carcinomas and papillary renal cell carcinoma [14]. Thanks to the consistent reactivity of neoplastic cells for cathepsin K in TFEB-rearranged renal cell carcinoma, it is easily distinguishable from the usual types of renal cell carcinomas [15]. Differentiating pure epithelioid PEComa/epithelioid angiomyolipoma from TFEB-rearranged renal cell carcinoma is challenging, as the two entities share the immunohistochemical expression of cathepsin K and melanocytic markers, such as HMB45 and Melan-A. PAX8 immunostaining and CD68 (PG-M1) negativity support the diagnosis of TFEB-rearranged renal cell carcinoma, whereas pure epithelioid PEComa/epithelioid angiomyolipoma has the opposite immunoreactivity, being negative for PAX8 and positive for CD68 (PG-M1) [16].

Among the renal tumors characterized by eosinophilic cells, cathepsin K is observed in eosinophilic solid and cystic renal cell carcinoma and high-grade oncocytic tumor/sporadic renal cell carcinomas with eosinophilic and vacuolated cells/eosinophilic vacuolated tumors, along with translocation renal cell carcinoma, which may mimic almost all subtypes of renal cell carcinoma because of the broad range of morphologies. On the other hand, the most common eosinophilic renal tumors (oncocytoma, eosinophilic variant of chromophobe renal cell carcinoma, and oncocytic papillary renal cell carcinoma) are considered negative for cathepsin K. However, a recent study describes the immunohistochemical expression of cathepsin K in a small series of oncocytoma (13 cases) and chromophobe renal cell carcinoma (13 cases) [17]. As the authors stated, the differences to the prior results may be explained by the use of a different clone (clone EPR19992). Although clone EPR19992 and clone 3F9 (the most used) were produced by the same manufacturer, the sequence and location of the epitope in this newer antibody are unknown. In our hands, oncocytoma and chromophobe renal cell carcinoma are negative for cathepsin K (clone 3F9). Focal staining (less than 5% of neoplastic cells) is observed in one of fifty-four oncocytomas and three of fifty-six chromophobe renal cell carcinomas. Overall, cathepsin K is helpful for recognizing these types of tumor entities and distinguishing them from other eosinophilic renal tumors most frequently encountered in daily clinical practice.

Finally, it is worth noting the presence of cathepsin K labeling in the capillaries and the associated macrophages in most renal cell neoplasms, as an internal control to evaluate the quality of the staining.

3. Conclusions

By exploring the novel insights into the cathepsin K expression, this review has the aim to highlight its usefulness in the differential diagnosis of renal tumors and to underline the relationship between cathepsin K and TFE3 translocations, TFEB translocation/amplification, and the cathepsin K and mTOR pathway (Figure 1). TFE3 hyperexpression resulting from *TFE3* gene translocation and the overexpression of TFEB due to either *TFEB* gene translocation or *TFEB* gene amplification cause cathepsin K expression [18]. On the other hand, inactivating mutations of *TSC1/TSC2* genes or activating mutations of the *mTOR* gene cause mTOR pathway activation, possibly resulting in cathepsin K expression [19][20][21].

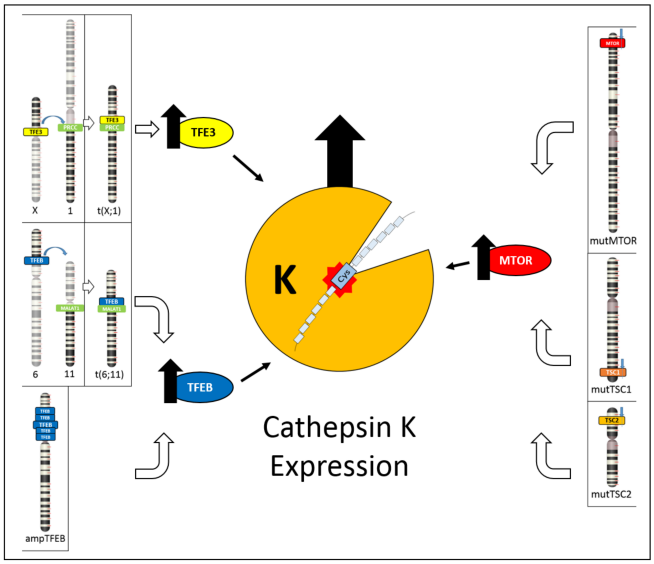

Figure 1. Schematic illustration showing the different mechanisms leading to cathepsin K expression. On the left, TFE3 hyperexpression due to *TFE3* gene translocation and TFEB hyperexpression due to either *TFEB* gene translocation or *TFEB* gene amplification cause cathepsin K expression. On the right, inactivating mutations of *TSC1/TSC2* genes or activating mutations of *mTOR* gene causes mTOR pathway activation, resulting in cathepsin K expression.

This aspect would be also interesting from a therapeutic point of view, especially in this era of personalized medicine, in which identifying biomarkers that can better predict response to therapy is crucial. mTOR inhibitors are an important pharmacological option for patients with tumors bearing TSC1/TSC2 mutations, and cathepsin K can be useful to detect these tumors. Understanding the precise interactions between cathepsin K and the mTOR pathway remains unknown and further studies are warranted to shed light on such mechanisms.

References

1. McGrath, M.E.; Klaus, J.L.; Barnes, M.G.; Bromme, D. Crystal structure of human cathepsin K complexed with a potent inhibitor. Nat. Struct. Biol. 1997, 4, 105–109.
2. Novinec, M.; Lenarcic, B. Cathepsin K: A unique collagenolytic cysteine peptidase. Biol. Chem. 2013, 394, 1163–1179.
3. Costa, A.G.; Cusano, N.E.; Silva, B.C.; Cremers, S.; Bilezikian, J.P. Cathepsin K: Its skeletal actions and role as a therapeutic target in osteoporosis. Nat. Rev. Rheumatol. 2011, 7, 447–456.
4. Garber, K. Two pioneering osteoporosis drugs finally approach approval. Nat. Rev. Drug Discov. 2016, 15, 445–446.
5. Troen, B.R. The regulation of cathepsin K gene expression. Ann. N. Y. Acad. Sci. 2006, 1068, 165–172.
6. Dai, R.; Wu, Z.; Chu, H.Y.; Lu, J.; Lyu, A.; Liu, J.; Zhang, G. Cathepsin K: The action in and beyond bone. Front. Cell. Dev. Biol. 2020, 8, 433.
7. Buhling, F.; Rocken, C.; Brasch, F.; Hartig, R.; Yasuda, Y.; Saftig, P.; Bromme, D.; Welte, T. Pivotal role of cathepsin K in lung fibrosis. Am. J. Pathol. 2004, 164, 2203–2216.
8. Runger, T.M.; Quintanilla-Dieck, M.J.; Bhawan, J. Role of cathepsin K in the turnover of the dermal extracellular matrix during scar formation. J. Investig. Dermatol. 2007, 127, 293–297.
9. Verbovsek, U.; van Noorden, C.J.; Lah, T.T. Complexity of cancer protease biology: Cathepsin K expression and function in cancer progression. Semin. Cancer Biol. 2015, 35, 71–84.
10. Reuter, V.E.; Argani, P.; Zhou, M.; Delahunt, B. Members of the IIiDUPG. Best practices recommendations in the application of immunohistochemistry in the kidney tumors: Report from the International Society of Urologic Pathology consensus conference. Am. J. Surg. Pathol. 2014, 38, e35–e49.
11. Zheng, G.; Martignoni, G.; Antonescu, C.; Montgomery, E.; Eberhart, C.; Netto, G.; Taube, J.; Westra, W.; Epstein, J.I.; Lotan, T.; et al. A broad survey of cathepsin K immunoreactivity in human neoplasms. Am. J. Clin. Pathol. 2013, 139, 151–159.
12. Gupta, S.; Argani, P.; Jungbluth, A.A.; Chen, Y.B.; Tickoo, S.K.; Fine, S.W.; Gopalan, A.; Al-Ahmadie, H.A.; Sirintrapun, S.J.; Sanchez, A.; et al. TFEB expression profiling in renal cell carcinomas: Clinicopathologic correlations. Am. J. Surg. Pathol. 2019, 43, 1445–1461.
13. Ross, H.; Martignoni, G.; Argani, P. Renal Cell Carcinoma With Clear Cell and Papillary Features. Arch. Pathol. Lab. Med. 2012, 136, 391–399.

14. Caliò, A.; Brunelli, M.; Segala, D.; Pedron, S.; Remo, A.; Ammendola, S.; Munari, E.; Pierconti, F.; Mosca, A.; Bollito, E.; et al. Comprehensive analysis of 34 MiT family translocation renal cell carcinomas and review of the literature: Investigating prognostic markers and therapy targets. Pathology 2020, 52, 297–309.
15. Caliò, A.; Segala, D.; Munari, E.; Brunelli, M.; Martignoni, G. MiT Family Translocation Renal Cell Carcinoma: From the Early Descriptions to the Current Knowledge. Cancers 2019, 11, 1110.
16. Caliò, A.; Brunelli, M.; Segala, D.; Pedron, S.; Tardanico, R.; Remo, A.; Gobbo, S.; Meneghelli, E.; Doglioni, C.; Hes, O.; et al. t(6;11) renal cell carcinoma: A study of seven cases including two with aggressive behavior, and utility of CD68 (PG-M1) in the differential diagnosis with pure epithelioid PEComa/epithelioid angiomyolipoma. Mod. Pathol. 2018, 31, 474–487.
17. Iakymenko, O.A.; Delma, K.S.; Jorda, M.; Kryvenko, O.N. Cathepsin K (Clone EPR19992) Demonstrates Uniformly Positive Immunoreactivity in Renal Oncocytoma, Chromophobe Renal Cell Carcinoma, and Distal Tubules. Int. J. Surg. Pathol. 2021.
18. Martignoni, G.; Bonetti, F.; Chilosi, M.; Brunelli, M.; Segala, D.; Amin, M.B.; Argani, P.; Eble, J.N.; Gobbo, S.; Pea, M. Cathepsin K expression in the spectrum of perivascular epithelioid cell (PEC) lesions of the kidney. Mod. Pathol. 2011, 25, 100–111.
19. Caron, A.; Richard, D.; Laplante, M. The Roles of mTOR Complexes in Lipid Metabolism. Annu. Rev. Nutr. 2015, 35, 321–348.
20. Kim, L.C.; Cook, R.S.; Chen, J. mTORC1 and mTORC2 in cancer and the tumor microenvironment. Oncogene 2017, 36, 2191–2201.
21. Han, J.; Wei, L.; Xu, W.; Lu, J.; Wang, C.; Bao, Y.; Jia, W. CTSK inhibitor exert its anti-obesity effects through regulating adipocyte differentiation in high-fat diet induced obese mice. Endocr. J. 2015, 62, 309–317.