

## REVIEW

# Evidence on the neural crest origin of PEComas

A. FERNANDEZ-FLORES

*Department of Anatomic Pathology, Hospital El Bierzo*

*Department of Cellular Pathology "PathCell",*

*Clinica Ponferrada, Ponferrada, Spain*

### Abstract

The perivascular epithelioid cell (PEC) has been proposed to be the proliferating cell type in a group of tumors known as PEComas. The histogenesis of PEComas is one of the most mysterious aspects of pathology. Hypothesis on its precursor are many, including a cell from blood vessel walls or the myoblast. In the current report, we review many morphologic, clinical, ultrastructural, molecular and genetic aspects that support the hypothesis of an origin of PEComas from the neural crest.

**Keywords:** perivascular migration, PEComa, "sugar" tumor, perivascular epithelioid cell, angiomyolipoma, neural crest.

### ☐ Introduction

The perivascular epithelioid cell (PEC) has been proposed to be the proliferating cell type in a group of tumors known as PEComas [1]. These so-called PEComas include angiomyolipoma, lymphangiomyoma, lymphangiomyomatosis, renal capsuloma, clear cell "sugar" tumor and clear cell myomelanocytic tumor [2, 3].

The histogenesis of PEComas is one of the most mysterious aspects of pathology. It has been proposed that they may originate from a precursor from blood vessel walls (Perivascular Epithelioid Cell) [4], maybe from the pericyte. Others say that they might have a myoblastic origin [5].

The hypothesis that they might originate from undifferentiate cells of the neural crest has also been mentioned in literature [6], although some are contrary to this, due to the lack of expression of S-100 by PEComas [7]. One should remember, nevertheless, how some cases of immunoexpression of S-100 by PEComas have been reported [8-10]. In this context, it is also interesting to remember the capacity of the cephalic neural crest, which gives origin to pericytes and smooth muscle cells of blood vessels of the face and the fore-brain [11], many of which do not express S-100 protein. Also, some other well recognized derivatives from neural crest do not express S-100 either, such as Merckel cells [12]. Therefore, such an expression is neither synonymous of "derivative from neural crest" nor a requisite to admit such an origin of a cellular lineage.

In the current report, we review many aspects that support the hypothesis of an origin of PEComas from the neural crest.

### ☐ Development of the neural crest and derivatives

Neural crests are bilaterally paired strips of cells

arising at the margins of the neural tube. They have a neuroectodermal origin and later they undergo an epithelial-mesenchymal transformation, subsequently exiting from the dorsal neural tube and migrating to different organs. Shortly after the neural tube is closed, the migration of cells from the neural crest begins. This happens in a head-to-tailward (rostrocaudal) sequence. The cells of the neural crest start by "delaminating" from the neuroepithelium, a fact to which some anatomic peculiarities probably contribute: for instance, the basement membrane surrounding the neural tube is discontinuous over its dorsal aspect [13].

Summarizing, there are many aspects that distinguish the migration of cells from the cranial neural crest and the one from the trunk neural crest. Cells from the latter migrate through two main paths: a dorsal pathway underneath the ectoderm, and a ventral pathway through the somites [14]. As a result, many structures that are currently recognized as derivatives from the neural crest will develop (Table 1).

In embryology, several techniques have been used to study if a cell population has a neural crest origin. For instance, the "cell-labeling" technique allows the visualization of the cell migration in developing embryos [15]. Melanocytes would be a recognized example of a neural crest derived cell population [16].

The problem in studying the origin of PEComas with such a technique is, that we are not aware so far, of a normal histological counterpart for these tumors. Assuming that they might develop from scanty residual perivascular cells, trapped in their migration from the neural crest, it would require a lot of luck to locate them. Moreover, it would be almost an act of faith to believe that those cells actually are a counterpart of PEComas.

However, there is indirect evidence, which supports the origin of PEComas from the neural crest.

**Table 1 – Cells derived from neural crest**

<b>Neuronal cells:</b>
<ul style="list-style-type: none"> <li>• Ganglion cells of the autonomic nervous system;</li> <li>• Spinal ganglia;</li> <li>• Sensory ganglia of cranial nerves (V, VII, IX and X).</li> </ul>
<b>Cells of the peripheral nervous system:</b>
<ul style="list-style-type: none"> <li>• Glial cells of the ganglia;</li> <li>• Schwann cells.</li> </ul>
<b>Supportive cells of the brain:</b>
<ul style="list-style-type: none"> <li>• Meninges (anterior brain).</li> </ul>
<b>Some cutaneous cells:</b>
<ul style="list-style-type: none"> <li>• Melanocytes;</li> <li>• Merkel cells.</li> </ul>
<b>Endocrine and paracrine system:</b>
<ul style="list-style-type: none"> <li>• Catecholaminergic adrenal cells;</li> <li>• Calcitonin-producing cells;</li> <li>• Type I cells of the carotidian body.</li> </ul>
<b>Mesectodermal derivatives:</b>
<ul style="list-style-type: none"> <li>• Facial dermis and cranial cartilage, bone, adipocytes and meninges;</li> <li>• Wall of large arteries (from the aortic arches);</li> <li>• Connective tissue of thymus and parathyroid gland;</li> <li>• Adipocytes within parasympathetic ganglia of the gut;</li> <li>• Peripheral nerve fibroblasts.</li> </ul>

### ❏ **Proof related to the immunohistochemical and morphological peculiarities of PEComas**

PEComas typically co-express melanocytic markers (such as HMB-45 [11, 12], melan-A [MART-1] [8] and microphthalmia transcription factor [MITF] [9]) and muscular markers (such as actin and less frequently desmin [8–10]) (Figure 1).

The expression of melanocytic markers is not aberrant but due to the presence of pre-melanosomes in the cells of PEComas [17–22]. There is evidence that cells that are derived from the neural crest can express many of the markers mentioned above, under certain environmental influence. It is well-known how the chief cell from pheochromocytomas (a tumor developed from a neural crest derivative) expresses HMB-45 [23]. It has been demonstrated that under the influence of TGF- $\beta$ , multipotential cells from the neural crest can differentiate to smooth muscle cells [24]. Also, studies of large series of neural crest-derived tumors have demonstrated that these can show expression of  $\alpha$ -smooth muscle actin on rare occasions [25]. Also, as a curiosity, some have published cases of malignant melanoma that showed differentiation to smooth muscle [26]. Neural crest cells can differentiate into smooth muscle cells *in vitro* in the presence of transforming growth factor (TGF)- $\beta$ 1 [27], folic acid [28], or when a specific type of culture medium is used [29].

In literature, there is a concept that the precursor of PEComas (whichever it is) has the capacity to modulate their morphology and phenotype, varying among a spindle cell (actin+, HMB-45+/-), an epithelioid cell (HMB-45+, actin+/-), or even to acquire a vacuolated morphology with an adipocyte-like appearance [6].

Admitting PEComas as derived from the neural crest could explain this morphologic variability and also its components of smooth muscle, melanocytic-like cells and adipocytes. For instance, it has been demonstrated how the multipotent, self-renewing neural crest-derived cells change intrinsic properties with time and location [30].

Some works on neural crest precursors isolated from the skin, have demonstrated that their differentiation *in vitro* resulted in the *de novo* generation of separate subpopulations of cells expressing neuronal, glial, smooth muscle and adipocyte markers [31].

Moreover, neural crest cells when cultured under the appropriate influences can differentiate into adipocytes [32]. A subset of adipocytes derives from the neural crest [32], such as the ones within the parasympathetic ganglia of the gut [33].

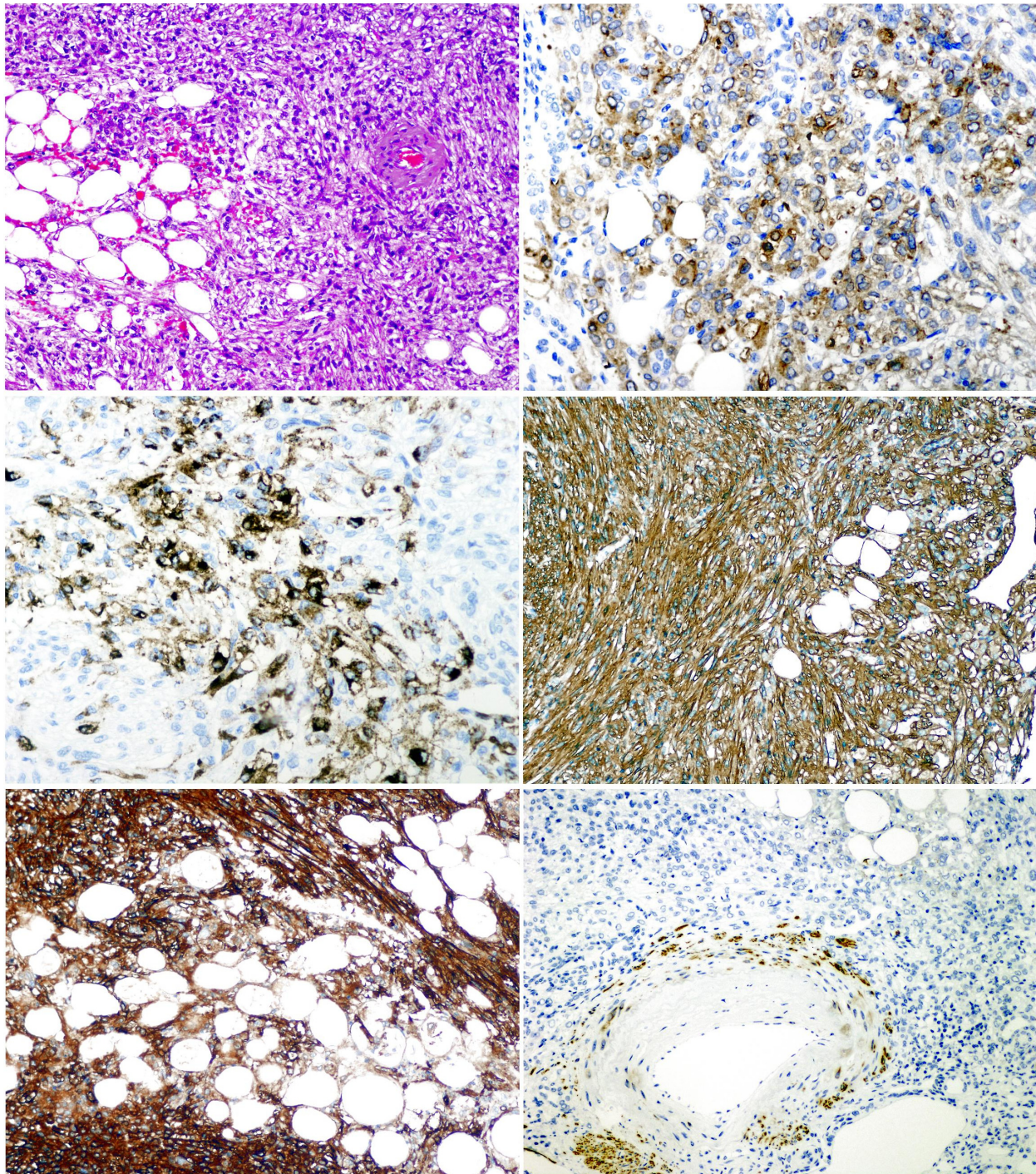
There is another interesting morphologic peculiarity of PEComas: their close relation to blood vessel walls. It is worth mentioning that a group has recently focused their attention on the phenomenon of the perivascular location of melanocytic nevi [34]. They proposed that such a phenomenon could be crucial in the histogenesis of melanocytic nevi [34]. If it was admitted that such a mechanism of migration was also used by the PEComa precursor when migrating from the neural crest, this would explain the intimate association of PEComas with the blood vessel wall [35]. In this way, in their migratory journey from the neural crest, the PEComa precursor might use (at least partly) the perivascular route. They would reach their final destination, acquiring their final phenotype... or not: some cells would remain trapped in the perivascular location in several organs. They would stay undifferentiated with capacity to express several markers under the environmental influence, such as smooth muscle, melanocytic or lipomatous markers. It was demonstrated years ago that similar undifferentiated precursors, derived from the neural crest, were present in many organs even in the adult life [36]. For instance, it has been discovered how the skin of adults has neural crest derived precursors that arise in skin during embryogenesis and persist into adulthood [37]. It has also been shown how these precursors have the ability to expand and differentiate into bone, cartilage, fat and muscle [38]. Curiously, there are cases of PEComas in literature, with an intense bone component, although it has been interpreted many times as metaplastic [39].

The fact that neural crest precursors could be the origin of certain tumors has already been suggested for some tumors and malformations of the skin and soft tissues, such as neurofibromas, melanocytic hamartomas, or some melanocytic nevi [40, 41].

Apart from melanocytic or muscular markers, there are other markers that link PEComas with the neural crest. Stem cell precursors have been recognized that can give rise to smooth muscle and melanocytes. These precursors express the neural stem cell markers NG2 and L1 [42–46]. Both markers have been found in angiomyolipomas [47].

From a genetic point of view, it should be mentioned that angiomyolipoma expresses a class of neural crest specifier genes, such as Snail, Twist1, Sox9 and FoxD3 [48].

On the other hand, some effector genes regulate neural crest differentiation by activating some cell-type-specific effectors including, for instance, c-Kit [49]. c-Kit is expressed in many cases by angiomyolipomas [50–52].



**Figure 1 – Renal angiomyolipoma showing several component of epithelioid cells and adipocytes. The tumor surrounds thick-walled blood vessels (top-left). The immunohistochemistry shows immunoexpression by the tumor of melanocytic markers such as Melan-A (top-right) or HMB-45 (second row, left). It also expresses muscular marker, such as smooth muscle actin (second row, right) or actin (bottom, left). Desmin is less commonly expressed, although blood vessel walls can be use as a reliable internal control (bottom right).**

#### ☐ Ultrastructural evidence

Some ultrastructural features are considered as indicative of a neural crest origin, such as neurite-like cytoplasmic processes, fine filaments and microtubules that are indistinguishable from those seen in normal neurites, synaptic-like structures, and neurosecretory-like vesicles [53].

Some have demonstrated how, in tissue cultures of angiomyolipoma, the cells exhibit long neurite-like processes, which are similar to neuritis [54]. Also,

microtubular have been found in “sugar” tumor [54]. Moreover, neurosecretory-type granules have been found in cases of “sugar” cell tumor of the lung [56–59].

#### ☐ Proof related to clinical peculiarities of PEComas

Another peculiarity of PEComas is their ubiquity. They have been described in many visceral and somatic locations, such as the kidney [60], urinary bladder [61], prostate [62], uterus [63], ovary [64], vagina [65], vulva

[55], lung [66], pancreas [67], liver [68], breast [69], soft tissues [70], skull base [71], gastrointestinal tract [72], oral mucosa [73], nasal cavity [74], bone, orbit, retroperitoneum [75], inter-atrial cardiac septum [76] and, of course, the skin [3].

An origin from the neural crest would explain such ubiquity since derivatives from neural crest are found in somatic as well as in visceral locations [14].

On the other hand, the association between angiomyolipomas and tuberous sclerosis is a well-known fact [6, 76–78]. Tuberous sclerosis is related to alterations in the *TSC1* and *TSC2* genes [79–83]. *TSC1* and *TSC2* encode hamartin (also known as tuberous sclerosis protein 1) and tuberin (or tuberous sclerosis protein 2), respectively. These are two cytosolic proteins that function together as a heterodimer participating in signaling pathways that control cell growth and proliferation [84]. Chromosomal alterations in *TSC1* and *TSC2* have even been found in hamartomas of patients with tuberous sclerosis [85].

Loss of heterozygosity (LOH) of chromosome arm 16p (containing the *TSC2* locus) was demonstrated in both the inherited and sporadic forms of angiomyolipomas [85]. LOH of the *TSC1* gene was also found in angiomyolipomas [85]. Also, other chromosomal alterations that involve *TSC1* and *TSC2* have been described in PEComas [86, 87]. Similar alterations of *TSC2* have been described in cases of lymphangiomyomatosis, which is included in the group of PEComas [88–92]. *TSC1* has also occasionally been involved in focal cortical dysplasia, which is due to alterations in cell migration from the neural crest [93, 94].

### ☐ Future lines of investigation

One of the difficulties in identifying the precursor cell of PEComas could lie in a simple fact: even when cells from the neural crests have reached their final destinations, a number of them remain undifferentiated, pluripotent and even endowed with the stem cell capacity of self-renewal [95]. The techniques of cell labeling, as commented above, are difficult to use with PEComas, since the normal histological counterpart is unknown. Therefore, more evidence supporting a neural crest origin for PEComas could be found from molecular and genetic proof. It is predictable, for instance, that PEComas express neural crest effector genes, such as PAX3 (the same way melanocytes do [96]), *D1x5* or *Msx1/2*. It is also predictable that neural crest specifiers genes are activated in PEComas. Examples are Sox10, Sox9, AP-2 and c-Myc [49]. Sox gene, for instance, has been implicated in melanocyte development and melanoma [97].

While c-myc expression was not relevant in some angiomyolipomas tested [98], in some others, a hormonal treatment has stimulated the expression of c-myc by tumoral cells in cases of lymphangiomyomatosis [99]. Also, some of the transcription factors mentioned above, are involved in the regulation of the MITF promoter, such as Pax3, CREB, Sox10, and Lef1 [100]. It is a well-known fact how MITF is expressed by

PEComas [101]. MITF also plays neural crest effector functions and is involved in the delamination and the regulation of adhesive properties [49], with a relevant role in the differentiation and/or the functional features of several cell types including osteoclasts, melanocytes, mast cells, and natural killer cells [102–104]. Therefore, some other similar neural crest effectors, such as P0, Connexin 32 (Cx32) or Trp, could be searched (and probably found) in PEComas.

The evidences supporting a hypothesis on the neural crest origin of PEComas are many. Such a hypothesis would clearly explain many of the peculiarities of these tumors.

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### References

- [1] Bonetti F, Martignoni G, Colato C, Manfrin E, Gambacorta M, Faleri M, Bacchi C, Sin VC, Wong NL, Coady M, Chan JK, *Abdominopelvic sarcoma of perivascular epithelioid cells. Report of four cases in young women, one with tuberous sclerosis*, Mod Pathol, 2001, 14(6):563–568.
- [2] Folpe AL, McKeeney JK, Li Z, Smith SJ, Weiss SW, *Clear cell myomelanocytic tumor of the thigh: report of a unique case*, Am J Surg Pathol, 2002, 26(6):809–812.
- [3] de Saint Aubain Somerhausen N, Gomez Galdon M, Bouffieux B, Courtin C, Theunis A, Vogeleer MN, Myant N, *Clear cell 'sugar' tumor (PEcoma) of the skin: a case report*, J Cutan Pathol, 2005, 32(6):441–444.
- [4] Hornick JL, Fletcher CD, *PEComa: what do we know so far?* Histopathology, 2006, 48(1):75–82.
- [5] Stone CH, Lee MW, Amin MB, Yaziji H, Gown AM, Ro JY, Têtu B, Paraf F, Zarbo RJ, *Renal angiomyolipoma: further immunophenotypic characterization of an expanding morphologic spectrum*, Arch Pathol Lab Med, 2001, 125(6):751–758.
- [6] Martignoni G, Pea M, Reghellin D, Zamboni G, Bonetti F, *PEComas: the past, the present and the future*, Virchows Arch, 2008, 452(2):119–132.
- [7] Pisharody U, Craver RD, Brown RF, Gardner R, Schmidt-Sommerfeld E, *Metastatic perivascular epithelioid cell tumor of the colon in a child*, J Pediatr Gastroenterol Nutr, 2008, 46(5):598–601.
- [8] Kim WJ, Kim SR, Choe YH, Lee KY, Park SJ, Lee HB, Chung MJ, Jin GY, Lee YC, *Clear cell "sugar" tumor of the lung: a well-enhanced mass with an early washout pattern on dynamic contrast-enhanced computed tomography*, J Korean Med Sci, 2008, 23(6):1121–1124.
- [9] Nakanishi K, Kawai T, Suzuki M, *Benign clear cell tumor of the lung. A histopathologic study*, Acta Pathol Jpn, 1988, 38(4):515–522.
- [10] Panizo-Santos A, Sola I, de Alava E, Lozano MD, Idoate MA, Pardo FJ, *Angiomyolipoma and PEComa are immunoreactive for MyoD1 in cell cytoplasmic staining pattern*, Appl Immunohistochem Mol Morphol, 2003, 11(2):156–160.
- [11] Etchevers HC, Vincent C, Le Douarin NM, Couly GF, *The cephalic neural crest provides pericytes and smooth muscle cells to all blood vessels of the face and forebrain*, Development, 2001, 128(7):1059–1068.
- [12] Skelton HG, Smith KJ, Hitchcock CL, McCarthy WF, Lupton GP, Graham JH, *Merkel cell carcinoma: analysis of clinical, histologic, and immunohistologic features of 132 cases with relation to survival*, J Am Acad Dermatol, 1997, 37(5 Pt 1):734–739.
- [13] Martins-Green M, Erickson CA, *Basal lamina is not a barrier to neural crest cell emigration: documentation by TEM and by immunofluorescent and immunogold labelling*, Development, 1987, 101(3):517–533.
- [14] Bronner-Fraser M, *Neural crest cell formation and migration in the developing embryo*, FASEB J, 1994, 8(10):699–706.

- [15] Le Douarin NM, *The avian embryo as a model to study the development of the neural crest: a long and still ongoing story*, Mech Dev, 2004, 121(9):1089–1102.
- [16] Dupin E, Le Douarin NM, *Development of melanocyte precursors from the vertebrate neural crest*, Oncogene, 2003, 22(20):3016–3023.
- [17] Pea M, Bonetti F, Zamboni G, Martignoni G, Riva M, Colombari R, Mombello A, Bonzanini M, Scarpa A, Ghimenton C *et al.*, *Melanocyte-marker-HMB-45 is regularly expressed in angiomyolipoma of the kidney*, Pathology, 1991, 23(3):185–188.
- [18] Pea M, Bonetti F, Zamboni G, Martignoni G, Fiore-Donati L, Doglioni C, *Clear cell tumor and angiomyolipoma*, Am J Surg Pathol, 1991, 15(2):199–202.
- [19] Weeks DA, Malott RL, Arnesen M, Zuppan C, Aitken D, Mierau G, *Hepatic angiomyolipoma with striated granules and positivity with melanoma-specific antibody (HMB-45): a report of two cases*, Ultrastruct Pathol, 1991, 15(4–5):563–571.
- [20] Bonetti F, Pea M, Martignoni G, Zamboni G, Iuzzolino P, *Cellular heterogeneity in lymphangiomyomatosis of the lung*, Hum Pathol, 1991, 22(7):727–728.
- [21] Gaffey MJ, Mills SE, Zarbo RJ, Weiss LM, Gown AM, *Clear cell tumor of the lung. Immunohistochemical and ultrastructural evidence of melanogenesis*, Am J Surg Pathol, 1991, 15(7):644–653.
- [22] Gal AA, Koss MN, Hochholzer L, Chejfec G, *An immunohistochemical study of benign clear cell ('sugar') tumor of the lung*, Arch Pathol Lab Med, 1991, 115(10):1034–1038.
- [23] Unger PD, Hoffman K, Thung SN, Pertsemilides D, Wolfe D, Kaneko M, *HMB-45 reactivity in adrenal pheochromocytomas*, Arch Pathol Lab Med, 1992, 116(2):151–153.
- [24] Abe K, *Therapeutic potential of neurotrophic factors and neural stem cells against ischemic brain injury*, J Cereb Blood Flow Metab, 2000, 20(10):1393–1408.
- [25] Dundr P, Povýsil C, Tvrdík D, *Actin expression in neural crest cell-derived tumors including schwannomas, malignant peripheral nerve sheath tumors, neurofibromas and melanocytic tumors*, Pathol Int, 2009, 59(2):86–90.
- [26] Banerjee SS, Bishop PW, Nicholson CM, Eyden BP, *Malignant melanoma showing smooth muscle differentiation*, J Clin Pathol, 1996, 49(11):950–951.
- [27] Shah NM, Groves AK, Anderson DJ, *Alternative neural crest cell fates are instructively promoted by TGFβ family members*, Cell, 1996, 85(3):331–343.
- [28] Boot MJ, Steegers-Theunissen RP, Poelmann RE, Van Iperen L, Lindemans J, Gittenberger-de Groot AC, *Folic acid and homocysteine affect neural crest and neuroepithelial cell outgrowth and differentiation in vitro*, Dev Dyn, 2003, 227(2):301–308.
- [29] Jain MK, Layne MD, Watanabe M, Chin MT, Feinberg MW, Siblinga NE, Hsieh CM, Yet SF, Stemple DL, Lee ME, *In vitro system for differentiating pluripotent neural crest cells into smooth muscle cells*, J Biol Chem, 1998, 273(11):5993–5996.
- [30] Wong CE, Paratore C, Dours-Zimmermann MT, Rochat A, Pietri T, Suter U, Zimmermann DR, Dufour S, Thiery JP, Meijer D, Beermann F, Barrandon Y, Sommer L, *Neural crest-derived cells with stem cell features can be traced back to multiple lineages in the adult skin*, J Cell Biol, 2006, 175(6):1005–1015.
- [31] Toma JG, McKenzie IA, Bagli D, Miller FD, *Isolation and characterization of multipotent skin-derived precursors from human skin*, Stem Cells, 2005, 23(6):727–737.
- [32] Billon N, Iannarelli P, Monteiro MC, Glavieux-Pardanaud C, Richardson WD, Kessaris N, Dani C, Dupin E, *The generation of adipocytes by the neural crest*, Development, 2007, 134(12):2283–2292.
- [33] Le Lièvre CS, Le Douarin NM, *Mesenchymal derivatives of the neural crest: analysis of chimaeric quail and chick embryos*, J Embryol Exp Morphol, 1975, 34(1):125–154.
- [34] Barnhill RL, Chastain MA, Jerdan MS, Lebbé C, Janin A, Lugassy C, *Angiotropic neonatal congenital melanocytic nevus: how extravascular migration of melanocytes may explain the development of congenital nevi*, Am J Dermatopathol, 2010, 32(5):495–499.
- [35] Fernandez-Flores A, *Perivascular migration: a clue to the histogenesis of PEComas?* Am J Dermatopathol, 2011, in press.
- [36] Kruger GM, Mosher JT, Bixby S, Joseph N, Iwashita T, Morrison SJ, *Neural crest stem cells persist in the adult gut but undergo changes in self-renewal, neuronal subtype potential, and factor responsiveness*, Neuron, 2002, 35(4):657–669.
- [37] Fernandes KJ, Toma JG, Miller FD, *Multipotent skin-derived precursors: adult neural crest-related precursors with therapeutic potential*, Philos Trans R Soc Lond B Biol Sci, 2008, 363(1489):185–198.
- [38] Hoogduijn MJ, Rakonczay Z, Genever PG, *The effects of anticholinergic insecticides on human mesenchymal stem cells*, Toxicol Sci, 2006, 94(2):342–350.
- [39] Menéndez CL, Gil Ugarteburu R, Capilla Ampudia JM, Corte Torres G, Fuente E, Argüelles M, *A case of pararenal PEComa with extensive bone metaplasia*, Virchows Arch, 2008, 452(3):349–350.
- [40] Zembowicz A, Mihm MC, *Dermal dendritic melanocytic proliferations: an update*, Histopathology, 2004, 45(5):433–451.
- [41] Philippon E, Chen S, *Unique case: syringocystadenoma papilliferum associated with an eccrine nevus*, Am J Dermatopathol, 2009, 31(8):806–807.
- [42] Nishiyama A, Lin XH, Giese N, Heldin CH, Stallcup WB, *Co-localization of NG2 proteoglycan and PDGF alpha-receptor on O2A progenitor cells in the developing rat brain*, J Neurosci Res, 1996, 43(3):299–314.
- [43] Ozerdem U, Grako KA, Dahlin-Huppe K, Monosov E, Stallcup WB, *NG2 proteoglycan is expressed exclusively by mural cells during vascular morphogenesis*, Dev Dyn, 2001, 222(2):218–227.
- [44] Grako KA, Ochiya T, Barritt D, Nishiyama A, Stallcup WB, *PDGF (alpha)-receptor is unresponsive to PDGF-AA in aortic smooth muscle cells from the NG2 knockout mouse*, J Cell Sci, 1999, 112(Pt 6):905–915.
- [45] Chekenya M, Hjelstuen M, Enger PO, Thorsen F, Jacob AL, Probst B, Haraldseth O, Pilkington G, Butt A, Levine JM, Bjerkvig R, *NG2 proteoglycan promotes angiogenesis-dependent tumor growth in CNS by sequestering angiostatin*, FASEB J, 2002, 16(6):586–588.
- [46] Arbiser JL, Yeung R, Weiss SW, Arbiser ZK, Amin MB, Cohen C, Frank D, Mahajan S, Herron GS, Yang J, Onda H, Zhang HB, Bai X, Uhlmann E, Loehr A, Northrup H, Au P, Davis I, Fisher DE, Gutmann DH, *The generation and characterization of a cell line derived from a sporadic renal angiomyolipoma: use of telomerase to obtain stable populations of cells from benign neoplasms*, Am J Pathol, 2001, 159(2):483–491.
- [47] Lim SD, Stallcup W, Lefkove B, Govindarajan B, Au KS, Northrup H, Lang D, Fisher DE, Patel A, Amin MB, Arbiser JL, *Expression of the neural stem cell markers NG2 and L1 in human angiomyolipoma: are angiomyolipomas neoplasms of stem cells?* Mol Med, 2007, 13(3–4):160–165.
- [48] Karbowniczek M, *Neural crest origin and notch-dependent cell-fate decision in tuberous sclerosis complex*, <http://www.thelamfoundation.org/assets/files/FridayAbstracts.pdf>, accessed August 2<sup>nd</sup>, 2010.
- [49] Meulemans D, Bronner-Fraser M, *Gene-regulatory interactions in neural crest evolution and development*, Dev Cell, 2004, 7(3):291–299.
- [50] Makhoulouf HR, Remotti HE, Ishak KG, *Expression of KIT (CD117) in angiomyolipoma*, Am J Surg Pathol, 2002, 26(4):493–497.
- [51] Zanelli M, Cortecchia S, Righi E, Caprara L, De Lillo M, Costa F, Galanti G, Bondi A, *Epithelioid angiomyolipoma of the kidney: case report*, Pathologica, 2008, 100(3):202–205.
- [52] Torii I, Kondo N, Takuwa T, Matsumoto S, Okumura Y, Sato A, Tanaka F, Nishigami T, Hasegawa S, Tsujimura T, *Perivascular epithelioid cell tumor of the rib*, Virchows Arch, 2008, 452(6):697–702.
- [53] Nikai H, Ijuhin N, Yamasaki A, Nutani K, Imai K, *Ultrastructural evidence for neural crest origin of the melanotic neuroectodermal tumor of infancy*, J Oral Pathol Med, 1977, 6(4):221–232.

- [54] Ashfaq R, Weinberg AG, Albores-Saavedra J, *Renal angiomyolipomas and HMB-45 reactivity*, Cancer, 1993, 71(10):3091–3097.
- [55] Tazelaar HD, Batts KP, Srigley JR, *Primary extrapulmonary sugar tumor (PEST): a report of four cases*, Mod Pathol, 2001, 14(6):615–622.
- [56] Becker NH, Soifer I, *Benign clear cell tumor ("sugar tumor") of the lung*, Cancer, 1971, 27(3):712–719.
- [57] Gaffey MJ, Mills SE, Frierson HF Jr, Askin FB, Maygarden SJ, *Pulmonary clear cell carcinoid tumor: another entity in the differential diagnosis of pulmonary clear cell neoplasia*, Am J Surg Pathol, 1998, 22(8):1020–1025.
- [58] Harbin WP, Mark GJ, Greene RE, *Benign clear-cell tumor ("sugar" tumor) of the lung: a case report and review of the literature*, Radiology, 1978, 129(3):595–596.
- [59] Hoch WS, Patchefsky AS, Takeda M, Gordon G, *Benign clear cell tumor of the lung. An ultrastructural study*, Cancer, 1974, 33(5):1328–1336.
- [60] Eble JN, *Angiomyolipoma of kidney*, Semin Diagn Pathol, 1998, 15(1):21–40.
- [61] Pan CC, Yu IT, Yang AH, Chiang H, *Clear cell myomelanocytic tumor of the urinary bladder*, Am J Surg Pathol, 2003, 27(5):689–692.
- [62] Pan CC, Liang WY, Huang CW, Chiang H, *Diagnosing minimal adenocarcinoma on prostate needle biopsy by real-time dynamic telepathology through the internet: evaluation of an economic technology for remote consultation*, Hum Pathol, 2002, 33(2):242–246.
- [63] Pea M, Martignoni G, Zamboni G, Bonetti F, *Perivascular epithelioid cell*, Am J Surg Pathol, 1996, 20(9):1149–1153.
- [64] Anderson AE, Yang X, Young RH, *Epithelioid angiomyolipoma of the ovary: a case report and literature review*, Int J Gynecol Pathol, 2002, 21(1):69–73.
- [65] Folpe AL, Mentzel T, Lehr HA, Fisher C, Balzer BL, Weiss SW, *Perivascular epithelioid cell neoplasms of soft tissue and gynecologic origin: a clinicopathologic study of 26 cases and review of the literature*, Am J Surg Pathol, 2005, 29(12):1558–1575.
- [66] Liebow AA, Castleman B, *Benign clear cell ("sugar") tumors of the lung*, Yale J Biol Med, 1971, 43(4–5):213–222.
- [67] Zamboni G, Pea M, Martignoni G, Zancanaro C, Faccioli G, Gilioli E, Pederzoli P, Bonetti F, *Clear cell "sugar" tumor of the pancreas. A novel member of the family of lesions characterized by the presence of perivascular epithelioid cells*, Am J Surg Pathol, 1996, 20(6):722–730.
- [68] Goodman ZD, Ishak KG, *Angiomyolipomas of the liver*, Am J Surg Pathol, 1984, 8(10):745–750.
- [69] Govender D, Sabaratnam RM, Essa AS, *Clear cell 'sugar' tumor of the breast: another extrapulmonary site and review of the literature*, Am J Surg Pathol, 2002, 26(5):670–675.
- [70] Fukunaga M, *Perivascular epithelioid cell tumor (PEComa) of soft tissue: case report with ultrastructural study*, APMIS, 2004, 112(2):98–104.
- [71] Lehman NL, *Malignant PEComa of the skull base*, Am J Surg Pathol, 2004, 28(9):1230–1232.
- [72] Birkhaeuser F, Ackermann C, Flueckiger T, Guenin MO, Kern B, Tondelli P, Peterli R, *First description of a PEComa (perivascular epithelioid cell tumor) of the colon: report of a case and review of the literature*, Dis Colon Rectum, 2004, 47(10):1734–1737.
- [73] Koutlas IG, Pambuccian SE, Jessurun J, Manivel JC, Gopalakrishnan R, *Perivascular epithelioid cell tumor of the oral mucosa*, Arch Pathol Lab Med, 2005, 129(5):690–693.
- [74] Banerjee SS, Eyden B, Trenholm PW, Sheikh MY, Wakamatsu K, Ancans J, Rosai J, *Monotypic angiomyolipoma of the nasal cavity: a heretofore undescribed occurrence*, Int J Surg Pathol, 2001, 9(4):309–315.
- [75] Lau SK, Marchevsky AM, McKenna RJ Jr, Luthringer DJ, *Malignant monotypic epithelioid angiomyolipoma of the retroperitoneum*, Int J Surg Pathol, 2003, 11(3):223–228.
- [76] van Baal JG, Smits NJ, Keeman JN, Lindhout D, Verhoef S, *The evolution of renal angiomyolipomas in patients with tuberous sclerosis*, J Urol, 1994, 152(1):35–38.
- [77] Debloom JR, Friedrichs A, Swick BL, Whitaker DC, *Management of cutaneous angiomyolipoma and its association with tuberous sclerosis*, J Dermatol, 2006, 33(11):783–786.
- [78] Chorianopoulos D, Stratakos G, *Lymphangioleiomyomatosis and tuberous sclerosis complex*, Lung, 2008, 186(4):197–207.
- [79] Janssen LAJ, Sandkuyl LA, Merckens EC, Maat-Kievit JA, Sampson JR, Fleury P, Hennekam RCM, Grosveld GC, Lindhout D, Halley DJJ, *Genetic heterogeneity in tuberous sclerosis*, Genomics, 1990, 8(2):237–242.
- [80] Nellist M, Brook-Carter PT, Connor JM, Kwiatkowski DJ, Johnson P, Sampson JR, *Identification of markers flanking the tuberous sclerosis locus on chromosome 9 (TSC1)*, J Med Genet, 1993, 30(3):224–227.
- [81] Vrtel R, Verhoef S, Bouman K, Maheshwar MM, Nellist M, van Essen AJ, Bakker PL, Hermans CJ, Bink-Boelkens MT, van Elburg RM, Hoff M, Lindhout D, Sampson J, Halley DJ, van den Ouweland AM, *Identification of a nonsense mutation at the 5' end of the TSC2 gene in a family with a presumptive diagnosis of tuberous sclerosis complex*, J Med Genet, 1996, 33(1):47–51.
- [82] van Slegtenhorst M, de Hoogt R, Hermans C, Nellist M, Janssen B, Verhoef S, Lindhout D, van den Ouweland A, Halley D, Young J, Burley M, Jeremiah S, Woodward K, Nahmias J, Fox M, Ekong R, Osborne J, Wolfe J, Povey S, Snell RG, Cheadle JP, Jones AC, Tachataki M, Ravine D, Sampson JR, Reeve MP, Richardson P, Wilmer F, Munro C, Hawkins TL, Sepp T, Ali JB, Ward S, Green AJ, Yates JR, Kwiatkowska J, Henske EP, Short MP, Haines JH, Jozwiak S, Kwiatkowski DJ, *Identification of the tuberous sclerosis gene TSC1 on chromosome 9q34*, Science, 1997, 277(5327):805–808.
- [83] Johnson MW, Emelin JK, Park SH, Vinters HV, *Co-localization of TSC1 and TSC2 gene products in tubers of patients with tuberous sclerosis*, Brain Pathol, 1999, 9(1):45–54.
- [84] Nellist M, van Slegtenhorst MA, Goedbloed M, van den Ouweland AM, Halley DJ, van der Sluijs P, *Characterization of the cytosolic tuberin-hamartin complex. Tuberin is a cytosolic chaperone for hamartin*, J Biol Chem, 1999, 274(50):35647–35652.
- [85] Carbonara C, Longa L, Grosso E, Mazzucco G, Borroni C, Garrè ML, Brisigotti M, Filippi G, Scabar A, Giannotti A, Falzoni P, Monga G, Garini G, Gabrielli M, Riegler P, Danesino C, Ruggieri M, Magro G, Migone N, *Apparent preferential loss of heterozygosity at TSC2 over TSC1 chromosomal region in tuberous sclerosis hamartomas*, Genes Chromosomes Cancer, 1996, 15(1):18–25.
- [86] Pan CC, Jong YJ, Chai CY, Huang SH, Chen YJ, *Comparative genomic hybridization study of perivascular epithelioid cell tumor: molecular genetic evidence of perivascular epithelioid cell tumor as a distinctive neoplasm*, Hum Pathol, 2006, 37(5):606–612.
- [87] Pan CC, Chung MY, Ng KF, Liu CY, Wang JS, Chai CY, Huang SH, Chen PC, Ho DM, *Constant allelic alteration on chromosome 16p (TSC2 gene) in perivascular epithelioid cell tumour (PEComa): genetic evidence for the relationship of PEComa with angiomyolipoma*, J Pathol, 2008, 214(3):387–393.
- [88] Smolarek TA, Wessner LL, McCormack FX, Mylet JC, Menon AG, Henske EP, *Evidence that lymphangioleiomyomatosis is caused by TSC2 mutations: chromosome 16p13 loss of heterozygosity in angiomyolipomas and lymph nodes from women with lymphangioleiomyomatosis*, Am J Hum Genet, 1998, 62(4):810–815.
- [89] Steagall WK, Taveira-DaSilva AM, Moss J, *Clinical and molecular insights into lymphangioleiomyomatosis*, Sarcoidosis Vasc Diffuse Lung Dis, 2005, 22 Suppl 1:S49–S66.
- [90] Carsillo T, Astrinidis A, Henske EP, *Mutations in the tuberous sclerosis complex gene TSC2 are a cause of sporadic pulmonary lymphangioleiomyomatosis*, Proc Natl Acad Sci U S A, 2000, 97(11):6085–6090.
- [91] Strizheva GD, Carsillo T, Kruger WD, Sullivan EJ, Ryu JH, Henske EP, *The spectrum of mutations in TSC1 and TSC2 in women with tuberous sclerosis and lymphangioleiomyomatosis*, Am J Respir Crit Care Med, 2001, 163(1):253–258.
- [92] Crooks DM, Pacheco-Rodriguez G, DeCastro RM, McCoy JP Jr, Wang JA, Kumaki F, Darling T, Moss J, *Molecular and genetic analysis of disseminated neoplastic cells in lymphangioleiomyomatosis*, Proc Natl Acad Sci U S A, 2004, 101(50):17462–17467.

- [93] Grajkowska W, Kotulska K, Matyja E, Larysz-Brysz M, Mander M, Roszkowski M, Domańska-Pakieła D, Lewik-Kowalik J, Jóźwiak S, *Expression of tuberin and hamartin in tuberous sclerosis complex-associated and sporadic cortical dysplasia of Taylor's balloon cell type*, *Folia Neuropathol*, 2008, 46(1):43–48.
- [94] Spalice A, Parisi P, Nicita F, Pizzardi G, Del Balzo F, Iannetti P, *Neuronal migration disorders: clinical, neuro-radiologic and genetics aspects*, *Acta Paediatr*, 2009, 98(3):421–433.
- [95] Le Douarin NM, Creuzet S, Couly G, Dupin E, *Neural crest cell plasticity and its limits*, *Development*, 2004, 131(19):4637–4650.
- [96] Medic S, Ziman M, *PAX3 expression in normal skin melanocytes and melanocytic lesions (naevi and melanomas)*, *PLoS One*, 2010, 5(4):e9977.
- [97] Harris ML, Baxter LL, Loftus SK, Pavan WJ, *Sox proteins in melanocyte development and melanoma*, *Pigment Cell Melanoma Res*, 2010, 23(4):496–513.
- [98] Röcken C, Schneider-Stock R, Buhtz P, Manger T, Roessner A, *Hepatic angiomyolipoma in a 26-year-old Caucasian woman with a history of tibial osteosarcoma*, *Pathol Res Pract*, 1999, 195(11):765–772.
- [99] Yu J, Astrinidis A, Howard S, Henske EP, *Estradiol and tamoxifen stimulate LAM-associated angiomyolipoma cell growth and activate both genomic and nongenomic signaling pathways*, *Am J Physiol Lung Cell Mol Physiol*, 2004, 286(4):L694–L700.
- [100] Goding CR, *Mitf from neural crest to melanoma: signal transduction and transcription in the melanocyte lineage*, *Genes Dev*, 2000, 14(14):1712–1728.
- [101] Chaplin A, Conrad DM, Tatlidil C, Jollimore J, Walsh N, Covert A, Pasternak S, *Primary cutaneous PEComa*, *Am J Dermatopathol*, 2010, 32(3):310–312.
- [102] Mansky KC, Sulzbacher S, Purdom G, Nelsen L, Hume DA, Rehli M, Ostrowski MC, *The microphthalmia transcription factor and the related helix-loop-helix zipper factors TFE-3 and TFE-C collaborate to activate the tartrate-resistant acid phosphatase promoter*, *J Leukoc Biol*, 2002, 71(2):304–310.
- [103] Mansky KC, Marfatia K, Purdom GH, Luchin A, Hume DA, Ostrowski MC, *The microphthalmia transcription factor (MITF) contains two N-terminal domains required for trans-activation of osteoclast target promoters and rescue of mi mutant osteoclasts*, *J Leukoc Biol*, 2002, 71(2):295–303.
- [104] Steingrimsson E, Tessarollo L, Pathak B, Hou L, Arnheiter H, Copeland NG, Jenkins NA, *Mitf and Tfe3, two members of the Mitf-Tfe family of bHLH-Zip transcription factors, have important but functionally redundant roles in osteoclast development*, *Proc Natl Acad Sci U S A*, 2002, 99(7):4477–4482.

#### Corresponding author

Angel Fernandez-Flores, MD, PhD, Department of Anatomic Pathology, Hospital El Bierzo; Department of Cellular Pathology "PathCell", Clinica Ponferrada, Avenida Galicia 1, 24400, Ponferrada, Spain; Phone (00 34) 987 423732, e-mail: gpyauflowerlion@terra.es

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