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Pulmonary lymphangioleiomyomatosis: A proposed state of neoplastic senescence

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ABSTRACT

Pulmonary lymphangioleiomyomatosis (PLAM) is a disease strongly associated with tuberous sclerosis. In PLAM patients, with and without clinical tuberous sclerosis, mutations in the tuberous sclerosis complex involving the proteins hamartin and tuberin have been found. These proteins are key regulators of the mTOR pathway. mTOR activation is a key step in normal cellular senescence. The hypothesis proposed here is that mutations in the tuberous sclerosis complex leading to mTOR activation result in the specialized LAM cells acquiring many of the cellular characteristics of the normal senescent cell, a state that I propose to characterize as a state of neoplastic senescence. Using this hypothesis as a theoretical basis, many of the enigmatic features of the pathogenesis and clinical behavior of PLAM can be explained. In addition, the hypothesis may lead to new insights into possible therapeutic interventions for this disease.

Hypothesis

The disease pulmonary lymphangioleiomyomatosis (PLAM) has long been an enigma. For many years it was classified as an interstitial lung disease with other forms of chronic inflammatory lung diseases leading to progressive destruction of the normal lung architecture and ultimately causing respiratory failure. However, key insights into the pathogenesis of this disease have led to the realization that PLAM is in fact a neoplastic process and calls have been made for the scientific community to “call it what it is”, a low grade destructive metastasizing neoplasm [1]. Nevertheless, it is quite understandable that there is some hesitation to fully accept this axiom. A number of issues make it difficult to fully ascribe to this dictum. First, if it is a neoplasm with metastatic spread to the lung, where is the primary site for this tumor? While there have been proposals and theories regarding this, a primary site has never been fully and universally recognized. Second, if it is a metastasizing neoplasm, why is the lung always bilaterally and symmetrically affected. There are no other examples of a neoplastic process in the lungs where the involvement is always and without exception diffuse, symmetric, and bilateral. Third, in typical neoplastic processes, with time, the neoplastic cells accumulate and form ever enlarging mass lesions. In PLAM, the disease may persist for decades, slowly destroying the lungs, but one never sees a dominant mass lesion. In all these respects, PLAM appears unique. The hypothesis proposed here is that mutations in the tuberous sclerosis complex leading to mTOR activation result in the specialized LAM cells acquiring many of the cellular characteristics of the normal senescent cell, a state that I propose to characterize as a state of neoplastic senescence. Acceptance of this concept will help solve all three of the enigmas that I have listed regarding the pathogenesis of this disease.

Body of text

The state of normal senescence has been well characterized and reviewed [2]. Cells are driven into senescence by activation of mTOR pathways in the presence of cell cycle inhibitors (p53, p16, pRb) and switched off important growth signals and cell replication. In addition, as cells enter senescence, they alter their metabolic and synthetic profiles and move to what has been called a senescence associated secretory phenotype (SASP). The senescence associated secretory proteins include a variety of cytokines, chemokines, and importantly for the pathogenesis of PLAM, pro-vasoformative factors, including VEGF, as well as tissue metalloproteinases and other digestive enzymes [3]. The presence of these digestive enzymes helps explain the normal senescence associated “emphysema” with loss of pulmonary tissues that is part of the normal aging process and play an important role in the digestion of pulmonary tissues in PLAM. Fully senescent cells enter into a state of permanent growth arrest, however, growth arrest and the SASP can be “uncoupled”. In addition, on the pathway to senescence there has been described a condition where cells are in a state of growth

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arrest, but retain "proliferative potential" [4]. Recognition of both of these states is important for the theory of PLAM as a state of neoplastic senescence. Although oncogene-induced senescence is an alternative route to the senescent state, the pathogenesis of the neoplastic senescence that I am proposing is not an oncogene driven pathway. Instead, what I propose is a metabolic pathway to senescence secondary to the same mutation in the TSC complex that leads to the neoplastic clone of LAM cells.

Mutations associated with PLAM have been well described in the key proteins hamartin and tuberin, integral components of the tuberous sclerosis complex (TSC) [5]. These proteins are important regulators of the normal mTOR pathway. I propose that mutations in these proteins alter the dynamics of cells entering into the senescent state. Although classic thinking suggests that once a cell enters the senescent state, that it is an irreversible process. However, as noted above, the growth arrest aspect of senescence and the SASP of senescence can be uncoupled. Furthermore, there appears to be a phase in the evolution of senescence where although there is a state of growth arrest, the cells retain proliferative potential. In a neoplastic senescence model of PLAM, this state of growth arrested but "not yet senescent" plays an important role. In tuberous sclerosis, a disease which is highly associated with PLAM in women, there is a germ line mutation in the TSC. In PLAM, this represents a "first hit" mutation but is not a sufficient mutation for the pathogenesis of PLAM. At a minimum, it has been proposed that a "second hit" mutation is required for the disease to evolve [6]. There are a staggering number of mutations described in the TSC (over 2000) and the type and location of mutations result in a variety of genotype/phenotype correlations [5]. For example, there are mutations that are not associated with tuberous sclerosis, but are associated with PLAM. Mutations in the tuberin component of the TSC are most strongly associated with PLAM, although mutations in hamartin have also been described. The TSC acts as an upstream inhibitory regulator of mTOR activity [7]. Mutations to the TSC that affect the ability of the complex to inhibit mTOR will result in unrestrained mTOR activity thereby promoting cellular senescence. Unrestrained mTOR activity is a well described feature of the senescent cell [2].

The reason a primary site for the neoplasm PLAM has been difficult to identify is also explainable by invoking the concept of neoplastic senescence. I propose the cells in the primary site are in a largely non-replicative growth arrested state, but a state that retains a proliferation potential. As a result, they do not grow to large sizes that would be readily recognizable on imaging scans or even on gross examination of specimens. Because PLAM is a disease that is nearly entirely restricted to women, and that even in patients with TS, males are only rarely reported to develop PLAM, this strongly suggests that the primary site for the tumor should be localized in the female genital tract. In fact, researchers have identified small inconspicuous lesions of LAM cells in the female genital tract of patients with PLAM [8]. Again, I will propose that the reason these primary tumors do not enlarge to recognizable tumor masses over the course of many years is that they have entered a largely growth arrested, but not a fully senescent state. Nevertheless, in this state the cells express the SASP, particularly the pro-angiogenic profile with VEGF expression among other factors which facilitate the LAM cells gaining access to the lymphatic drainage and also allowing them to again have a limited proliferation phase before re-entering a largely growth arrested senescent phase.

The necessary conditions for these LAM cells in the female genital tract to gain access to lymphatic spaces, resume replication, metastasize to regional lymph nodes and eventually migrate to the lung have not been defined. In a previous publication I have proposed that PLAM follows a disease pathogenesis similar to lymphangitic carcinomatosis [9]. With the female genital tract as the primary site for the tumor, and lymphangitic spread as the route by which the metastatic LAM cells reach the lungs, it becomes necessary to postulate an obstructive lesion at the outlet of the thoracic duct to explain the unique feature of this metastatic disease that the involvement of the lungs is always diffuse, symmetric, and bilateral. The obstruction to egress of the LAM cells from the lymphatic drainage sets up a situation where there is backup of pressure in the lymphatics and retrograde flow of lymph fluid (containing the LAM cells) into the nearest drainage bed, which is the lungs. The retrograde flow into the lungs is fairly evenly distributed to both right and left lobes of lungs, again consistent with the observed pattern of distribution of disease in PLAM.

Critics of this proposed theory of pathogenesis might rightly point out that in typical cases of lymphangitic carcinoma involving the lung one cannot readily identify tumor cells in lymphatic spaces that run along the bronchovascular structures in the lung and along the pleural lymphatics. In cases of lymphangitic carcinomatosis involving the lung one can also readily recognize a lymphatic pattern of distribution of the disease with a microscopic low power objective. Neither of these can be done in histologic sections of PLAM. Again, in my prior publication, I have explained that the reason for this "apparent" lack of association with pulmonary lymphatics is due to the unique properties of the LAM cell. The LAM cells do not destroy the lung by "mass effect". Rather the destruction of the lung is via an enzymatic proteolytic destruction of the lung. LAM cells have been demonstrated to secrete a variety of proteolytic enzymes including tissue metalloproteinases 1, 2 and 9 [10] as well as cathepsin K [11]. Secretion of these enzymes break down the lymphatic walls allowing the LAM cells to escape the lymphatic routes and settle in a random distribution throughout the lung parenchyma. This pathogenesis also explains the high rate of pneumothorax associated with this disease. LAM cells that reach the pleural lymphatics before digesting the lymphatic walls can then proceed to digest sections of pleural tissues leading to pneumothorax. The secretion of these digestive enzymes is very similar to what has been described as the senescence associated secretory response, where secretion of tissue metalloproteinases are consistently upregulated [3].

Once the LAM cells have escaped the lymphatic routes that they follow en route to the lungs. I propose that the LAM cells enter into a state of neoplastic senescence characterized by growth arrest and a continued SASP. This is why we do not see large tumor masses in the lung, despite the disease progressing over many years. Like pulmonary emphysema related to cigarette smoking, the disease proceeds by piecemeal digestion of the lung over many years. The molecular steps involved in the transition from growth arrested cells to fully senescent cells with a SASP remains to be investigated. I propose that the LAM lesions in the female genital tract are growth arrested cells which under the appropriate conditions express the SASP with a predominant pro-angiogenic phenotype allowing these cells access to the lymphatic drainage system with subsequent spread to lymph nodes and eventually to the lung. This model would predict that once in the lymphatic fluid, these growth arrested cells with "proliferative potential" would then revert to a limited proliferative phase, possibly due to stimulatory factors present in the lymphatic fluids. However, once they have been transported through the lymphatic spaces to the lungs, digested through the lymphatic channels, and migrated into the pulmonary parenchymal tissues, they then enter a state of neoplastic senescence characterized by growth arrest and expression of the SASP. As stimulation of lymphatic proliferation is a feature of the LAM cells, it is likely that on re-entry into lymphatic spaces, the cells could again go through a limited proliferation phase. In this way, a self-perpetuating cycle would ensue which leads to progressive enzymatic destruction of the lungs through expression of the SASP but with only limited growth of the tumor cells.

In this brief article, I have hypothesized a new and perhaps unique pathogenetic mechanism of neoplasia to explain the enigma of PLAM. There are a number of issues that still remain unexplained. What are the necessary conditions/mutations for the neoplastic cells in the female genital tract to gain access to the lymphatic routes and begin proliferation? Once in the lung what are the drivers of the SASP which leads to the disruption of lymphatics and digestion of the lungs? What are the signals for these peculiar LAM cells to move from the growth arrested "not yet senescent phase" to a largely growth arrested phase?

This theory of “neoplastic senescence” helps explain many of the enigmas of this unusual neoplastic disease. In addition, this proposal has the potential to open new lines of investigation into the pathogenesis of PLAM. Additional therapeutic approaches to PLAM might become available should one discover the mechanisms whereby the senescence associated secretory response is activated. For example, IL-1 has been recently identified as a factor that upregulates the SASP, making it a potential target for therapies aimed at reducing the expression of the digestive enzymes leading to pulmonary destruction in PLAM [12].

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Declaration of Competing Interest

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References

[1] McCormack FX, Travis WD, Colby TV, Henske EP, Moss J. Lymphangioleiomyomatosis: calling it what it is: a low-grade, destructive, metastasizing neoplasm. Am J Respir Crit Care Med 2012;12:1210–2.
[2] Wiley CD, Campisi J. From ancient pathways to aging cells – connecting metabolism and cellular senescence. Cell Metab 2016;23(6):1013–21.
[3] Coppe J-P, Desprez P-Y, Krtolica A, Campisi J. The senescence-associated secretory phenotype: the dark side of senescence. Annu Rev Pathol 2010;5:99–118.
[4] Blagosklonny MV. Cell cycle arrest is not yet senescence, which is not just cell cycle arrest: terminology for TOR-driven aging. Aging 2012;4(3):159–65.
[5] Curatolo P, Moavero R, Roberto D, Graziola F. Genotype/phenotype correlations in tuberous sclerosis complex. Semin Pediatr Neurol 2015;22:259–73.
[6] Krymskaya VP, McCormack FX. Lymphangioleiomyomatosis: a monogenic model of malignancy. Annu Rev Med 2017;68:69–83.
[7] Huang J, Manning BD. The TSC1-TSC2 complex: a molecular switchboard controlling cell growth. Biochem J 2008;412(2):179–90.
[8] Hayashi T, Kumasaka T, Mitani K, Terao Y, Watanabe M, Oide T, et al. Prevalence of uterine and adnexal involvement in pulmonary lymphangioleiomyomatosis: a clinicopathologic study of 10 patients. Am J Surg Path 2011;35:1776–85.
[9] Asao S, Lombard CM, Tsau P. Pulmonary lymphangioleiomyomatosis with parietal pleural involvement: a case report with discussion of pathogenesis using pulmonary lymphangitic carcinomatosis as a model. Hum Path: Case Rep 2019;15:88–91.
[10] Matsui K, Takeda K, Yu ZX, Travis WD, Moss J, Ferrans VJ. Role for activation of matrix metalloproteinases in the pathogenesis of pulmonary lymphangioleiomyomatosis. Arch Pathol Lab Med 2000;124:267–75.
[11] Chilosi M, Pea M, Martignoni G, Brunelli M, Gobbo S, Poleti V, et al. Cathepsin-K expression in pulmonary lymphangioleiomyomatosis. Mod Pathol 2009;22:161–6.
[12] Lau L, Porciuncula A, Yu A, Iwakura Y, David G. Uncoupling the senescence-associated secretory phenotype from cell cycle exit via interleukin-1 inactivation unveils its protumorigenic role. Mol Cell Biol 2019;39(12). pii: e00586-18.