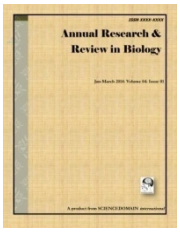

Annual Research & Review in Biology
4(1): 20-37, 2014

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Pulmonary Arterial Hypertension and Cancer: An Update on Their Similarities

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Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

Review Article

Received 13th June 2013
Accepted 21st August 2013
Published 4th October 2013

ABSTRACT

Pulmonary arterial hypertension (PAH) is characterized by an increase resistance of the vascular wall from pulmonary arteries leading to vascular lumen occlusion, right ventricular failure, and death. PAH has been described for many years, as a cardiovascular disease affecting the lungs. Whatever the initial cause, pulmonary arterial hypertension involves the vasoconstriction of blood vessels connected to and within the lungs. In addition, the increased workload of the heart causes hypertrophy of the right ventricle, making the heart less able to pump blood through the lungs, causing right heart failure. Recently several groups have demonstrated that PAH is a disease of excess proliferation and impaired apoptosis similar to neoplasia. Although the fundamental cause remains elusive, many predisposing and disease-modifying abnormalities occur, including endothelial injury/dysfunction, bone morphogenetic protein receptor-2 gene mutations, decreased expression of the K+ channel (Kv1.5), transcription factor activation [hypoxia-inducible factor-1 (HIF-1)], expression of survivin, and increased expression/activity of both serotonin transporters and platelet-derived growth factor receptors. Together, these abnormalities create a cancer-like, proliferative, apoptosis-resistant phenotype. From these observations, it has been established some similarities between PAH and cancer.
Therefore, in this review, we will discuss the essential alterations in pulmonary arterial hypertension as compared to cancer cell which has been alluded to as the "cancer

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paradigm". Based on these similarities, we can imagine that future therapies used to treat cancer could also work for PAH.

Keywords: Pulmonary arterials; pulmonary arterial hypertension (PAH); apoptosis; proliferation; cancer.

ABBREVIATIONS

Bcl2: B-cell lymphoma 2; BMPRII: Bone morphogenetic protein receptor II; EC: Endothelialcells; SML: Smooth muscle cells; DCA: Dichloroacetate; EGF: Epidermal growth factor; ET-1: Endothelin type 1; FGF: Fibroblast growth factor; HIF1α: Hypoxia-inducible factor 1-alpha; HIV: Human immunodeficiency virus; PAH: Pulmonary arterial hypertension; IAP: Inhibitor of apoptosis; MAPK: Mitogen-activated protein kinase; NFAT: Nuclear factor of activated T-cells; PDGF: Platelet-derived growth factor; PDH: Pyruvate dehydrogenase; PDK: Pyruvate dehydrogenase Kinase; SOD2: Superoxyde dismutase 2; STAT3: Signal transducer and activator of transcription 3; TGFβ: Transforming growth factor; VEGF: Vascular endothelial growth; PH: Pulmonary hypertension.

1. INTRODUCTION

PAH is a disease of the pulmonary vasculature defined by a resting mean Pulmonary Artery Pressure (PAP) superior at 25 mmHg and Pulmonary Vascular Resistance (PVR) superior at 3 Woods units [1]. At the « World Pulmonary Hypertension Symposium » in 2003, the term PAH for "Pulmonary Arterial Hypertension" has replaced the initial term "primary pulmonary arterial hypertension" [2]. More recently, a new epidemiology classification by the World Health Organization has been established for Pulmonary Hypertension (PH) [3] (Table 1). There are five categories of PH: (1) PAH; (2) PH associated with left-sided heart disease; (3) PH associated with lung disease/hypoxia; (4) thromboembolic PH; and (5) miscellaneous (Table 1). The present review focuses on category 1 (PAH), which includes idiopathic and familial PAH, as well as PAH associated with a variety of conditions, pulmonary veno-oclusive disease, pulmonary capillary hemangiomatosis, and persistent pulmonary hypertension of the newborn (Table 1). PAH is a syndrome in which pulmonary arterial obstruction increases pulmonary vascular resistance, which leads to right ventricular failure and therefore death of the patient [4]. Rai et al. in their review « The Cancer Paradigm of Severe Pulmonary Arterial Hypertension » from 2008, have proposed that PAH is a disease of excess proliferation and impaired apoptosis sharing some homology to neoplasia [5]. Several groups have also suggested that the abnormalities observed in PAH are similar to those observed in cancer [5-8]. The main observations are: (1) an excess of proliferation of smooth muscle cells (SMC) [9,10] and endothelial cells (EC) [11] from PAH patients, (2) a resistance to apoptosis of SMC [12], and (3) an increased expression of cancer markers expressed in pulmonary vessels [8,13]. These results bring an emerging paradigm in PAH pathology and could give the possibility to combine the therapeutic strategies used in cancer to treat PAH. A good example is the tyrosine-kinases inhibitor, Imatinib, the first anti-cancer drug which has been used to treat PAH (in phase III of clinical trial) [14]. Hanahan and Weinberg in their reference paper «The hallmarks of cancer » [15] have proposed that the transformation of a normal cell to a cancer cell require the acquisition of six properties: (1) self-sufficiency in growth signals, (2) insensitivity to growth inhibitors, (3) evasion to apoptosis, (4) limitless of replicative potential, (5) sustained angiogenesis, and (6) tissue invasion and metastasis. To be complete, we need to add to this list the new properties from

Hanahan and Weinberg update's [16]: (7) the metabolic energetic modifications and (8) evading immune response. Since these properties are shared by almost all cancer types, we will focus only on the similarities between PAH and cancer through the 8 properties listed above.

2. THE EIGHT PROPERTIES

2.1 Self-Sufficiency in Growth Signals

The transition from quiescent cells to proliferative cells involves the presence of growth signals, which are transduced to the cells through growth factors receptors. As compared to normal cells, cancer cells can produce their own growth signals [15,16]. It has been suggested by different groups [17,18] that the EGFR (Epidermal Growth Factor Receptor) could participate in PAH. The involvement of these receptors is also found in many cancers [19,20]. However it seems that the participation of EGFR from PAH is controversial. Dahal et al. [21] have suggested that EGFRs do not represent a promising target for the treatment of pulmonary hypertension. Further studies will be necessary to explain these discrepancies. In parallel, Platelet-Derived Growth Factor (PDGF) as like Epidermal Growth Factor (EGF) has been shown to stimulate Smooth Muscle Cells (SMC) proliferation and may be involved in the vascular changes observed in PAH. PDGF is a potent mitogen involved in the proliferation and migration of pulmonary vascular SMC [22]. It has been reported that the PDGF receptor antagonist Imatinib (STI571) reverses advanced pulmonary vascular disease in two animal models of pulmonary hypertension [22]. The antagonist prevents phosphorylation of the PDGF receptor and suppresses activation of downstream signaling pathways. Moreover, the expression of the PDGF receptor was found to be significantly increased in lung tissue from PAH patients compared with healthy donor lung tissue [23]. This selective antagonist has been also used for the first time in 2005 to treat a 61-years old woman with PAH [24]. A multicenter phase II evaluating the safety and efficacy of imatinib mesylate in PAH was recently completed. This study included 59 patients with PAH, who remained symptomatic on one or more standard PAH therapies, and in whom the safety and tolerability of a 400 mg dose of imatinib was evaluated. However, this study did not meet the pre-specified efficacy endpoint of change in 6 min walk distance. Nonetheless, the potential of the drug was reaffirmed on this basis and statistically significant improvements in hemodynamic endpoints, including both a significant decrease in pulmonary vascular resistance and a significant increase in cardiac output were observed [24]. A subgroup analysis of the most severely affected patients suggests even more robust improvements in exercise and hemodynamic variables [25]. These results are awaiting validation in a larger follow-up phase III, randomized, controlled trial, which is in the early stages of implementation. Tyrosine kinase inhibitors may represent a promising class of compounds for the future treatment of PAH. However, caution should be taken with kinase inhibitors. Indeed, it has been reported that dasatinib (a highly potent BCR-ABL kinase inhibitor) could induced severe precapillary PAH [26]. Although clinical improvement was generally observed after withdrawal of dasatinib, some patients remained symptomatic and showed persistent hemodynamic impairment several months after discontinuation of this agent. Even if PAH is a rare complication in patients treated with dasatinib, the increased use of dasatinib will certainly increase the number of patients at risk of developing PAH. Another study measuring the effect of soranefib (inhibitor of multiple kinases, including Raf-1, VEGF-R2, and PDGFR-β) in PAH patients, observed evidence of pharmacodynamic interactions—apparent sorafenib-induced resolution of common epoprostenol-associated skin flushing and the absence of systemic blood pressure elevations associated with inhibition of the VEGF-

signaling pathway [27]. Therefore, there are still a number of issues, such as the safety and tolerability profile, which need to be addressed.

PAH is in part due to hypertrophy and hyperplasia of pulmonary artery SMC and it has been suggested that PDGF could also participate as such phenomena via the activation of the Na+/H+ exchanger in response to growth factors [23,28] . In addition, PDGF has also been suggested to regulate tumor formation during cancer. The occurrence of clinically useful PDGF receptor antagonists used to treat cancer highlights the importance of PDGF receptor signaling in cancer malignancies [29]. Many cancer cells acquire the ability to synthesize growth factors to which they are responsive, creating autocrine stimulation [15]. Some of these growth factors are found to be overexpressed such as endothelin-1 (ET-1) [30], the Vascular Endothelial Growth Factor (VEGF). The increased secretion of these factors activates a cascade of growing factors responsible of the hyper-proliferation observed in cells of PAH patients [6]. So far, Endothelin-1 antagonists (i.e. Bosantan) influence endothelial function and are used in the treatment of PAH [31-34]. Moreover, diverse receptor families, including growth factors that act through receptor tyrosine kinases [e.g., EGF, and PDGF] or acting through G protein-coupled receptors (e.g., endothelin) [35], transduce their signals mainly by activating Mitogen-Activated Protein Kinase (MAPK) signal transduction pathways [36]. Accordingly, these pathways exert a profound effect on cell physiology, MAPK have been found activated in cancer [37], but also have been suggested to contribute to PAH pathology. The expression of MAPK, as well as PDGF, has been found to be increased in a genome wide RNA expression profiling in human lung from PAH [38]. The involvement of this signal transduction pathway in PAH remains to characterize to determine if its activation would be a cause or consequence of PAH.

2.2 Insensitivity to Growth Inhibitors

Within a normal tissue, multiple antiproliferative signals operate to maintain cellular quiescence and tissue homeostasis; these signals include both soluble growth inhibitors and immobilized inhibitors embedded in the extracellular matrix and on the surfaces of nearby cells. Cancer cells are insensitive to these antiproliferative signals. At the molecular level, the effects of the soluble signaling molecule Transforming Growth Factor (TGFβ) are the best documented [15,39]. Cancer cells lose the antiproliferative effect of TGFβ in favor of a stimulating activity [15]. As described previously, PAH can be idiopathic, heritable or associated with drug or toxin exposure or other conditions such as connective tissue diseases, human immunodeficiency virus infection, congenital heart diseases, and portal hypertension. Genetic studies in PAH have revealed heterozygous germline mutations in the Bone Morphogenetic Protein Receptor II (BMPR-II), a receptor for the TGFß. These mutations are detected in 10 to 40% of idiopathic PAH and in 58% to 74% of patients with a family history of PAH [40-42]

BMPR-II mutation in pulmonary artery SMC contributes to abnormal growth responses to BMPR-II ligands (BMP 2, 6 and 7). The reduced expression or function of BMPR-II signaling leads to exaggerated TGF-ß signaling and altered activation of intracellular signaling via the Smad pathway [43]. The reduction of expression or function of BMPRII contributes to the control of cell growth in cancer [39] [44] but also in PAH [43,45]. The regulation of TGF-ß signaling in cellular pathogenesis of PAH may provide new approaches to our understanding of some aspects of lung disease in particular in patients with a family history of PAH.

2.3 Evasion to Apoptosis

Under various stress conditions, normal cells initiate their death by inducing intracellular apoptotic signaling. It is very well recognized that apoptosis resistance is one of the main characteristic of cancer [15,16]. Two family genes have been described to regulate apoptosis, the B-Cell Leukemia protein-2 (Bcl2) family [46] and the Inhibitors of Apoptosis Protein (IAP) [43]. The anti-apoptotic protein Bcl2 is found to be overexpressed in many cancers [46,47], but also in patients with PAH [48,49]. In SMC, McMurtry et al. have shown that survivin, belonging to IAP family, was express in PAH patients [13]. Survivin expression is mitosis dependent, therefore suggesting a role in cell proliferation [46]. As mentioned previously in 'Insensivity to growth inhibitors' one of the essential PAH characteristics is the lost of signaling mediated by BMPRII receptor. This observation is even more interesting when we look in details the effect of the Bone morphogenetic proteins (BMPs), which are a group of growth factors. BMPs have a dual role: to inhibit the SMC proliferation but also to induce cell apoptosis [12].

The major role of miRNAs in pulmonary arterial remodeling is still relatively unknown although research data is emerging apace. The expression of miR-204 is found to be down-regulated in tumor tissue from gastric cancer patients [50]. miR-204 directly targets Bcl-2 [50]. With regard to pulmonary remodeling, miR-204 was first observed to be dysregulated in the monocrotaline and hypoxic rat model of PAH with levels of miR-204 down-regulated in the lungs from the disease model [51] as well as in the hypoxic mouse lung [52]. *In situ* hybridization demonstrated localization of miR-204 in SMC and its expression was reduced in SMCs from PAH patients, accompanied by increased levels of proliferation and lower levels of apoptosis. Additionally, treatment of monocrotaline rats with synthetic miR-204 mimic significantly lowered pulmonary artery pressure and medial wall thickness in small pulmonary arteries [52]. The miR-17/92 cluster is also highly involved in controlling tumor growth via regulation of proliferation and apoptosis [53] and another cell cycle regulator, cyclin-dependent kinase inhibitor 1A (p21), is also targeted by miR-17. The miR-17/92 cluster was first identified to be involved in tumor development [54]. Inhibition of miR-17 in rat model of PAH caused a reduction in systolic right ventricular pressure and pulmonary vascular remodeling [55]. The exact mechanisms through which this miRNA cluster are acting are still relatively unknown, therefore further knowledge must be gained before we can understand the true role of this cluster in PAH. The miR-34a is thought to be involved in various cancer pathways [56,57]. Over-expression of miR-34a leads to a reduction in proliferation and increase apoptosis [58,59]. A study by Mizuno et al. [60] demonstrated that hypoxia up-regulates p53 and in turn miR-34a. Accordingly, p53 knockout mice display an exaggerated PAH phenotype with increased systolic right ventricular pressure, and medial wall thickening in small pulmonary arteries when exposed to hypoxia [60]. Notch1 has been verified as a direct target for miR-34a [61], thus over-expression of miR-34a down-regulates Notch1 and its downstream targets Bcl-2 and Survivin [58,62], both of which are anti-apoptotic. Although the majority of studies reporting the p53/miR-34a/Notch1 pathway have examined the role in cancer, the pathogenesis of cancer and remodeling share several common features, however, further studies will confirm if the same response is initiated in pulmonary artery cells. Another miRNA thought to be involved in remodeling is miR-206. MiR-206 is down-regulated in SMCs from hypoxic mice and human SMCs proliferation and migration is reduced with over-expression of miR-206, along with increases in smooth muscle cell markers therefore promoting the contractile phenotype. Furthermore, human SMCs over-expressing miR-206 demonstrate increased apoptotic activity [63], indicating that lowered expression of miR-206, as in the case during PAH and hypoxia, promotes excessive proliferation and resistance to apoptosis. Little is known about miR-206 in disease

development with previous studies showing its involvement in regulation of breast cancer cell lines [64].

Many others abnormalities contribute to the apoptosis resistance observed in PAH patients: decreased of the potassium channels in SMCs [65], abnormal transduction of the apoptotic pathways in SMCs [66], increased expression of STAT3 and NFAT in SMCs [49] transcription factors, … Therefore, apoptosis resistance seems to be a determinant characteristic of PAH.

2.4 Limitless of Replicative Potential

Hayflick et al. have demonstrated that the replicative potential of primary cells in culture is limited with two following steps: senescence and crisis [67]. Senescence is a process by which cells stop to proliferate after few doubling passages, until they reach crisis. Cells die during crisis but some of them survive crisis and continue to proliferate [68,69]. These proliferating cells are characterized by two principal abnormalities: immortality and monoclonality [68]. Monoclonal cell population originates from one single cell with acquired proliferative advantages from its genomic instability [70]. Some studies have shown in PAH, endothelial cell expansion [71] but also somatic mutations [72]. These studies demonstrate a somatic genetic alteration similar to those observed into neoplasic lesions [71]. The evidence of a post-senescent phenotype in endothelial cells has been highlighted by studies on plexiform lesion from PAH patients [70,71]. These monoclonal cells, characterized by genomic instability, developed plexiform lesions (demonstrating an escape to senescence) similarly to cancer cells. Morphologic characteristics of severe PAH are plexiform lesions: complex, glomeruloid-like vascular structures originating from the pulmonary arteries. Whether plexiform lesions represent just a morphologic indicator lesion or play a role in the pathogenesis and/or progression of PAH has not yet been clarified. Plexiform lesion has been described as a proliferating network of endothelial-lined vascular channels supported by a core of specialized and apoptosis-resistant myofibroblasts, smooth muscle cells, or even undifferentiated mesenchymal cells. It has been reported recently, that some features of plexiform lesions resemble neoplastic disorders, and there is a striking resemblance to glomeruloid-like lesions in glioblastomas, however, the cellular composition and signaling differed significantly from those in PAH [73]. Plexiform lesions have been shown to have a distinct cellular composition and microenvironment, which contribute to the plexiform phenotype and set them apart from other processes of vascular remodeling in patients with PAH [73].These results suggest that the clonal expansion in PAH is a property that can be illustrated by a loss of contact inhibition conducting to absence of limit in replicative cellular potential. However, the plexiform lesions cannot be found in approximately two thirds of the patients and the genomic instability reported seems to be restricted to endothelial cells.

2.5 Sustained Angiogenesis

Oxygen and nutrients provided by vessels are crucial for cellular functions and survival [15]. Therefore, proliferative cells from tissue have the intrinsic capacity to induce the growth of blood vessels cells. Tumoral cells stimulate the formation of new blood vessels, by increasing the expression of angiogenic growth factors [74,75]. Angiogenesis is regulated by both inhibiting and activating signals, such as VEGF and Fibroblast Growth Factor (FGF). Many tumors have been found to overexpress VEGF and FGF [15] and their increased expression has also been observed in PAH. Indeed, pulmonary arterial SMCs and endothelial cells from PAH both expressed high levels of VEGF and EGF [6,76]. To conclude, angiogenesis seems also to be one of PAH property.

2.6 Invasion and Metastasis

During human cancer development, tumoral cells can colonize another organ to generate a second tumor referred as metastasis [15]. So far, metastasis has never been observed in PAH. Cells from PAH do not have this capacity to invade tissue as compared to cancer cells.

2.7 Metabolic Energetic Modifications

Dr Otto Warburg, in the mid-thirties, discovered « the main biochemical cause » of cancer, or what differentiates a cancer cell from a normal, healthy cell. Cancer cells have the capacity to consume high level of glucose as compared to normal cells [77]. Normal cells take in oxygen through their mitochondria. The mitochondria use oxygen to break up carbohydrate molecules (glucose) and release energy; however cancer cells seem to bypass mitochondria. Instead, they get energy from a process called glycolysis, in which energy is extracted from glucose without the use of oxygen [78], conducting to a “pseudo-hypoxic” state. This high level of glycolysis has been called later the “Warburg effect”, and since, this effect has been largely studied in many cancer types [79]. This glycolitic environment is also associated with apoptosis resistance. Indeed, many glycolitic enzymes are anti-apoptotic [80], such as Glycogen Synthase Kinase 3β (GSK-3β) which is inhibited during glycolysis and involved in proliferative diseases like cancer [81]. The glycolitic rate of cells from PAH patients, endothelial and SMCs, is 3 times higher than normal cells [82-84] showing a mitochondrial dysfunction identical to the bioenergetics changes observed in cancer [79]. The glucose increased observed in PAH can be explained either by i) an increase of hexokinase II (HXKII), the enzyme necessary for the first step of glycolysis, which phosphorylates the glucose [81], or ii) the fact that glycolysis is less efficient than oxidative mitochondrial phosphorylation to produce ATP for the cells. By homology to cancer cells, in PAH the mitochondria are also hyperpolarized in SMCs [13,49,65,85]. However the mechanisms responsible of this hyperpolarisation remain unclear and complex, involving intrinsic and extrinsic factors. Nevertheless, recently studies have suggested a deregulation between glucose and fatty acid production (Randle cycle) that could influence the glycolytic environment and the mitochondrial hyperpolarisation, and thus would increase the apoptosis induce by mitochondria [83].

Surprisingly little is known about the specific mechanisms underlying right ventricular hypertrophy and right ventricular dysfunction in the setting of PAH. Chronic pressure overload, as occurs in PAH, stimulates right ventricular hypertrophy. While the obvious approach to reducing right ventricular hypertrophy and right ventricular failure is to treat the underlying pulmonary arterial disease, recent experimental evidence suggests that the right ventricle can be therapeutically targeted in PAH [86]. In right ventricular hypertrophy phosphodiesterase-5, is selectively re-expressed. Inhibiting this enzyme (i.e. by sildenafil) enhances right ventricle contractility without affecting the left ventricle [27] which lacks phosphodiesterase-5. In contrast to the normal right ventricle, metabolism in right ventricular hypertrophy is reliant on glucose metabolism [87]. In hypoxia-induced PAH, expression of the glucose transporter GLUT4 is significantly increased in the right ventricle, suggesting a metabolic switch to glycolysis. New evidence shows that the right ventricle in PAH is glycolytic, due in part to activation of Pyruvate Deshydrogenase Kinase (PDK), and behaves as hibernating myocardium, demonstrating enhanced glucose oxidation and improved contractility in response to dichloroacetate [88]. Future PAH therapies should consider the effects of agents on both the right ventricle and the pulmonary vasculature.

In tumor cells, since mitochondrial activity is reduced, the enzyme Superoxide Dismutase 2 (SOD2) activity/expression is reduced therefore there is less radical oxygen species produced during this pseudo-hypoxic state and HIF1α (Hypoxia Inducible Factor 1 α) is activated. HIF1α targets the PDK. Kim *et al*. have postulated that the activation of PDK coupled to the inhibition of the Pyruvate DesHydrogenase (PDH) are responsible of the Warburg effect [89]. Altogether these effects induce the decreased expression of the potassium channels (Kv1.5), the depolarisation of the membrane and an increased of potassium and calcium cytosolic levels. This oncogenic deregulation of the metabolic pathway SOD2/HIF1α/PDK/PDH induced an increase proliferation and decrease apoptosis, and is also found in SMCs from PAH [65,85,90]. However, the activation SOD2/HIF1α/PDK/PDH by the Reactive Oxygen Species (ROS) (increase *vs.* decrease) is still very controversial [91-96], also the molecular origin of ROS production (mitochondria *vs* Nicotinamide Adenine Dinucleotide Phosphate (NADPH) oxidase) remains unclear.

The NFAT (Nuclear Factor of Activated T-cells)-Kv1.5 metabolic pathway has been recently demonstrated to be important for cancer, but also in SMCs from PAH [49,85]. The increased production of vasoconstrictors (endotheline, 5-HT, etc...) induces an increase of the intracellular calcium levels which in turns activates the transcription factor NFAT, reduces the expression of the potassium channels (Kv1.5) and inhibits apoptosis. In cancer as well as PAH, the increase of the membrane potential and the decrease of the channels Kv1.5, seems to contribute to the hyper-proliferation and the resistance to apoptosis observed in cells.

Mitochondria cannot explained by themselves the deregulations observed in PAH, however the mitochondrial metabolism offer an etiological explanation of the pathology based on the exhaustive number of studies on metabolic changes responsible of the «oncogenic» phenotype.

2.8 Evading Immune Destruction

Over the past few years, the manipulation of genes involved in the determination of various immune cell types, together with pharmacological inhibitors of such cells has shown them to play diverse and critical roles in cancer but also in PAH [97,98]. Inflammation has been defined as a complex series of interactions among soluble factors and cells. Recruitment of inflammatory cells such as leucocytes, macrophages, and lymphocytes abound in the complex vascular lesions of PAH [99,100] suggest that the inflammatory response is not confined to plexiform lesions but also observed in other vascular lesions of PAH. A growing list of signaling molecules released by inflammatory cells have been involved in PAH. These include growth factors such as VEGF, PDGF, TGF-alpha, FGF, and EGF; in addition some transcriptional factors such as NFAT, and HIF-1alpha. VEGF, a mediator of angiogenesis and also a factor involved in permeability and inflammatory processes of the vascular endothelium could play a central role in PAH [6]. Indeed VEGF has been found to be highly expressed in endothelial cells from PAH [6]. In parallel, active PDGF induces receptor dimerisation and activation followed by phosphorylation events involving sequential activation of MAPK cascades. These events not only play a role in cell proliferation but also in inflammation. The pathogenic role of PDGF in human PAH has been demonstrated by increased expression of PDGF and its receptors from patients with severe PAH [101], justifying latter on the use of inhibitors targeting PDGF in development for PAH patients, as mentioned previously in 'Self-sufficiency in growth signals'. There is also evidence for a general imbalance in TGFbeta signaling in PAH, for instance, loss of function mutation of the TGFbeta receptor has been linked to PAH in patients [72,102]. Others growth factors such

as FGF has been shown also to be up regulated in patients with pulmonary hypertension [103] and recently, it has been proposed as a new signaling axis involved in SMCs and endothelial cells from PAH [104]. The transcription factor NFAT by itself increases the transcription of multiple inflammatory mediators, such as interleukins and tumor necrosis factor. NFAT also activates T and B cells [105]. Importantly, NFAT is up regulated and activated in circulating inflammatory cells in patients with PAH [49] linking the modification in energetic metabolism to inflammation, both phenomena observed in PAH.

3. DISCUSSION

PAH is a disease of pulmonary vascular remodeling leading to increased pulmonary vascular resistance and reduced compliance. Neomuscularisation of non-muscular arteries and formation of plexiform and neointimal lesions can also occur.

Many studies described PAH as a cellular disorder which favors cell growth, angiogenesis and resistance to apoptosis … This cellular disorder seems to share some homology to cancer cells, which let to postulate that PAH phenotype is very similar to neoplasia [8,65,106]. The transformation of a normal cell to a cancer cell require the acquisition of 8 properties : (1) self-sufficiency in growth signals, (2) insensitivity to growth inhibitors, (3) evasion to apoptosis, (4) limitless of replicative potential, (5) sustained angiogenesis, (6) tissue invasion and metastasis (7) the metabolic modifications and (8) evading immune destruction necessary to tumorigenesis.

The vast majority of these cancer properties (seven out of eight) are also shared by pulmonary vascular cells from PAH patients (Fig. 1). Overall these cellular dysfunction can recapitulate in some extend a phenotype close to cancer cells: self-sufficiency in growth signals, insensitivity to growth inhibitors, evasion to apoptosis, metabolic modifications such as the “bioenergetics metabolism” in favor of glycolysis (Warburg Effect) and decrease of mitochondrial oxidation. Some analogies can be made between PAH and cancer cells. However, cancer cells as compared to PAH cells have the particular capacity to colonize another organ to generate a second tumor, metastasis [15]. Therefore, even few mechanisms similar between PAH and cancer, can help for a better understanding of the cellular deregulations observed in PAH, nevertheless PAH is not a cancer disease. In fact, PAH cells could be an intermediate cell type between normal cell and cancer cell.

Table 1. Clinical Classification of pulmonary hypertension

1. Pulmonary arterial hypertension (PAH)
    - 1.1. Idiopathic PAH
    - 1.2. Heritable:
        - 1.2.1. BMPR2
        - 1.2.2. ALK1, endoglin (with or without hereditary hemorrhagic telangiectasia
        - 1.2.3. Unknown
    - 1.3. Drugs and toxins-induced
    - 1.4. Associated with:
        - 1.4.1. Connective Tissue diseases
        - 1.4.2. HIV infection
        - 1.4.3. Portal hypertension
        - 1.4.4. Congenital heart diseases
        - 1.4.5. Schistosomiasis
        - 1.4.6. Chronic hemolytic anemia

1.5. Persistent pulmonary hypertension of the newborn
1.6 Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
2. Pulmonary hypertension due to left heart disease
2.1. Systolic dysfunction
2.2 Diastolic dysfunction
2.3. Valvular heart disease
3. Pulmonary hypertension due to lung diseases and/or hypoxemia
3.1. Chronic obstructive pulmonary disease
3.2. Interstitial lung disease
3.3. Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4. Sleep-disordered breathing
3.5. Alveolar hypoventilation disorders
3.6. Chronic exposure to high altitude
3.7. Developmental abnormalities
4. Chronic thromboembolic pulmonary hypertension
5. Pulmonary hypertension with unclear multifactorial mechanisms
5.1. Hematologic disorders: myeloproliferative disorder, splenectomy
5.2. Systemic disorders sarcoidosis, pulmonary langerhans cell histiocytosis : lymphangiomatosis, neurofibromatosis, vascultis
5.3. Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4. Others: tumoral obstruction, fibrosing, mediastintis, chronic renal failure on dialysis

Adapted from Simonneau et al. [3]

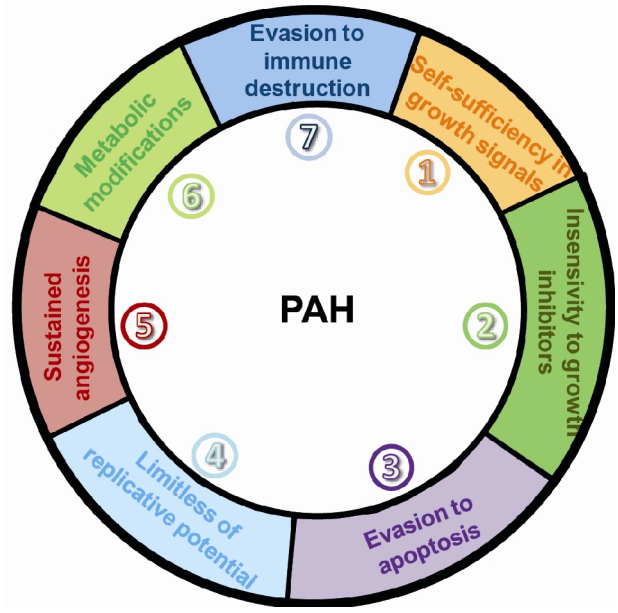

Fig. 1. The «cancer phenotype» in PAH. The effects observed in PAH recapitulate seven out of eight cancer properties proposed by Hanahan and Weinberg [15,16]

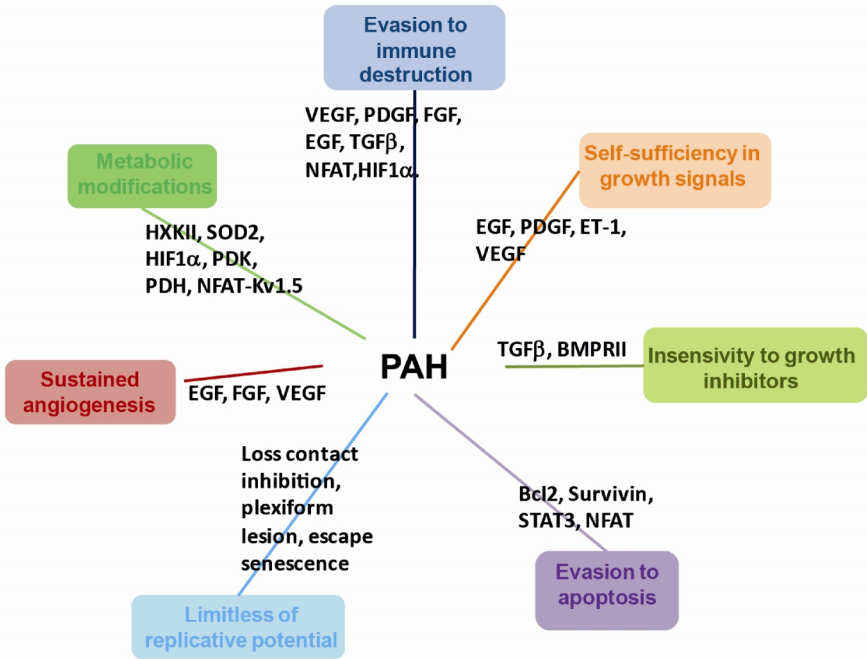

Fig. 2. The main proteins described to be differentially regulated in PAH and involved in the seven major cellular dysfunctions (non exhaustively). All these cellular functions are linked to basic cellular mechanisms essential for tumor cell survival and proliferation

4. CONCLUSION

The increase proliferation and the resistance to apoptosis in smooth muscle and endothelial cells play a key role in PAH, nevertheless PAH is a multifactorial disease which remains poorly understood. Indeed during PAH, many physiological changes have been observed such as vasoconstriction, in situ thrombosis, chronic inflammation, pulmonary vascular remodeling, and molecular, hormonal and genetic abnormalities.

Although the PAH is governed by some of the cancer hallmarks (Figs. 1 and 2) described by Hanahan and Weinberg [15,16], the absence of data on acquired capability, specifically tissue invasion, metastasis, and sustained angiogenesis, reveal that it is impossible to categorize PAH as an oncogenic view. However, according to the high level of death observed in PAH patients, it is essential to explore the different avenues to found novel innovative therapeutics. Thus, we believe that the great interest to study this «oncogenic» phenotype is to 1) better understand the cellular dysfunctions of this multifactorial disease, and 2) propose, potentially, some therapies already developed in cancer to treat PAH.

MAIN KEY POINTS

- Vascular lesion from PAH presents some of oncogenic properties : self-sufficiency in growth signals, insensitivity to growth inhibitors, evasion to apoptosis, limitless of replicative potential, sustained angiogenesis, the metabolic cellular modifications, and inflammation.

- Vascular lesion from PAH do not present metastasis or tissue invasion therefore they do not belongs to cancer but are an intermediate cell type between normal cells and cancer cells.
- Similarities between vascular cells from PAH patients and cells from cancer patients have some functional characteristics interesting to follow, with the aim to assess some cancer treatment as potential PAH treatments.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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