Pulmonary arterial hypertension: are we close to the success?

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Introduction

Pulmonary arterial hypertension (PAH) is a rare, but deadly disease. Despite the expansion of the therapeutic avenues, the treatment options are very limited and the survival rate continues to be inadequately low [1,2]. Once initiated by some vasculature insulting stimuli such as bacterial, viral, drug, or environmental toxins on the background of genetic abnormalities, the disease transforms from the initial damage to a complex response. This includes metabolic reprogramming, activation of various pro-survival pathways, initiation of the innate and adaptive immune systems and recruitment of stem and progenitor cells to the site of the damage [3,4]. The events described above were proposed to drive the transition of normal pulmonary vascular cells to cells with a highly proliferative phenotype [5] similar to the malignant transformation, which could not be controlled by the regular growth inhibitory mechanisms [6].

Interestingly, PAH development and progression seems to have a sequential nature of events that occur when initial damage is gradually followed by inflammation, repair, metabolic changes, fibrotic changes and uncontrolled proliferation. However, the exact sequence and duration of these overlapping stages may vary from patient to patient and depends on many factors, such as age, gender, previous history of health problems, etc. Unfortunately, such a complicated pattern of pathological events and mechanisms, many of which are still having to be identified, significantly complicate and diffuse our understanding of the disease [7]. A novel approach that will allow us to gain a better understanding is necessary in order to advance the current situation and increase our ability to transfer the knowledge accumulated in animal models to clinics.

The angio-proliferative models of PAH, which are reproducing the histo-pathological changes seen in human lungs, along with rodent genetic models, have brought necessary advantages to the PAH field [8]. However, in attempt to replicate the advanced stage of human PAH, most of the studies perform the analysis when the disease has already been fully developed. Thus, the important information about the mechanisms responsible for initiation, early progression, and transformation to the PAH phenotype is still not fully accounted for. Nevertheless, since the pathologic events in PAH keep changing with the progression of the disease, it is essential to recognize the mediators involved in PAH pathogenesis on each chronological step. The identification of these key players will ensure that the applied therapy will target the needs of the patient and will precisely attenuate the mechanisms involved at the moment of treatment.

Although it would not seem realistic currently, the cooperative efforts of the scientific community could and have already started bringing us closer to applying a precise approach for PAH treatment [9]. Thus, it could be anticipated that each of the chronologic stages of PAH possesses a unique profile of factors that could serve as a blueprint of the specific phase of the disease. By pinpointing these factors using different types of "omics" technology it is possible to elaborate the therapeutic targets specific for each phase of PAH. Once applied and tested in animal models, this approach can be later verified in humans. Of course, the findings made in animals cannot be expected to be fully translated to clinics due to a number of limitations including the contribution of concomitant disorders to the development of PAH in humans. However, by starting to move in this direction, it is possible to discover and re-discover effective therapeutic approaches.

The precision targeting of the midpoint pathways can bring back on board the therapies that were considered ineffective due to their broad application. In many clinical trials, there is some percent of the patients that have shown a positive response to the tested therapy [10,11]. These responders may represent individuals which received an adequate therapy based on their current pathological profile. However, since the therapeutic was tested in all patients without taking into account the PAH phenotype, the analysis of the efficiency of this new treatment in many cases confirms that the majority of the patient cohort was non-responsive or show only mild and transient response [12] .

Such a "non-personalized" approach can also explain the vast difference in the efficacy of the treatment in pre-clinical and clinical studies. Indeed, in the genetically homogeneous animals subjected to the standard procedure that aligns the coherence and extent of the animal response, the adequately selected therapy would show a low variability and a high effectivity. It is much harder to achieve the same effect in a genetically and phenotypically diverse human population.

Moreover, since the patients are classified based on the symptoms, like high pulmonary pressure and right ventricle dysfunction, and not the actual pathogenic mechanisms that are responsible for the manifestation of these symptoms, the same group of patients may consist of individuals with a completely different PAH phenotype. Thus, it is not surprising that many clinical trials fail to confirm the efficiency of the same molecule in such a diverse patient cohort. The situation, however, could be improved by an accurate phenotyping of PAH patients, which will increase the homogeneity of study cohorts and efficiency of treatment [9].

Overall, it seems pivotal to the future success of the field to further understand how we can better classify the stages of PAH progression, find the key pathological targets for each stage and apply the precise, molecular-based classification to the clinics in order to match the specific treatment needs of each patient.

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