招請講演

IL-1

○ Lisa Mielniczuk

IL-2

エンドセリン受容体の構造と機能

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肺動脈性肺高血圧症の治療ターゲットの 1 つに、エンドセリン経路がある。血管内皮細胞で産生される 21 残基のペプチドホルモン、エンドセリン -1 (ET-1) は、血管平滑筋細胞のエンドセリン A 型および B 型 (ET_A, ET_B) 受容体や血管内皮細胞の ET_B受容体に作用する。前者は血管収縮作用を、後者は血管弛緩作用をもたらし、両者のバランスによって局所血流は調節されている。G タンパク質共役型受容体である ET_Aおよび ET_B受容体のリガンド選択性や情報伝達の分子機構を理解して構造を基盤とする創薬を推進させる目的で、ET-1 結合型および非結合型 ET_B受容体の X 線結晶構造解析を行った。本質的に構造柔軟性が高く結晶化が困難な ET_B受容体について、熱安定化変異体を開発することによってその構造解析に成功した。複合体構造では、ET-1 が受容体にすっぽりとはまり込んで広い領域で相互作用し、そのカルボキシ末端部分が受容体内部結合ポケットに深く潜り込んで、特異的な相互作用を形成していた。変異受容体のリガンド結合実験や ET-1 結合型および非結合型構造の比較から、リガンド選択性や ET-1 結合によるシグナル伝達様式について議論したい。

IL-3

Right heart adaption to pulmonary arterial hypertension: physiology and pathobiogy

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Pulmonary arterial hypertension (PAH) results from profound remodeling of the distal lung vessels leading irremediably to death through right ventricular (RV) failure. PAH (Group 1 of the World Classification of pulmonary hypertension) can be idiopathic (IPAH) or associated with other disorders such as connective tissue diseases. Prominent among the latter is systemic sclerosis (SSc), a heterogeneous disorder characterized by endothelium dysfunction, dysregulation of fibroblasts resulting in excessive collagen production, and immune abnormalities. For reasons unknown so far, SSc-associated PAH (SSc-PAH) carries a significantly worse prognosis compared to any other form of PAH in Group 1 including IPAH. We have previously shown that patients with SSc-PAH have a median survival of only 3-4 years, compared to approximately 8 years for IPAH, despite modern PAH therapy. We have taken advantage of this discrepancy in survival between these two groups to compare their demographics, functional performance, intrinsic cardiac performance and analysis of RV-pulmonary vascular coupling, and response to therapy, to shed some light on pathogenic mechanisms in this syndrome. As death is principally due to RV failure, we speculated that RV adaptation to PAH differed between the two entities due to disparate pulmonary artery (PA) loading, perhaps from vessel stiffening, or intrinsic RV myocardial disease that might limit function and adaptation to increased afterload. In SSc, RV function may also be impaired by inflammatory processes, excess fibrosis of the myocardium, or altered angiogenesis, which may all contribute to impaired contractile reserve exacerbating cardio-pulmonary impedance mismatch. Our research group has recently established that, while pulmonary vascular load may be similar between IPAH and SSc-PAH patients, the latter patients display significantly reduced myocardial contractility as assessed by pressure-volume loop measurements. The response to exercise also varies between these two groups of patients with PAH.
This talk will focus on fundamental hemodynamic, structural, and functional differences in RV performance between patients with SSc-PAH compared to IPAH, which may account for survival discrepancies between the two populations. In addition, possible underlying pathologic basic mechanisms are discussed. Specifically, newly identified serum biomarkers which may predict survival and be determined by genetic predisposition will be discussed along with their possible implications in the pathogenesis of the adaptation of the RV to increased load in PAH, which has long been recognized as the leading cause of death in these patients.

IL-4

Highlights from Basic Research to Therapy in PAH

○ Christophe Guignabert
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Pulmonary arterial hypertension (PAH) is a hemodynamic state defined by a resting mean pulmonary arterial pressure (mPAP) at or above 25 mm of mercury (Hg) with a normal pulmonary capillary wedge pressure, ultimately leading to right heart failure and premature death. Although considerable progress has been made in the development of therapies for PAH, there is no drug available specifally targeting the cellular accumulation into the pulmonary artery vessel wall, a key pathological feature that contributes to the progressive narrowing of the lumen ultimately leading to right ventricle hypertrophy and dysfunction.
Because numerous important discoveries in the PAH pathogenesis have been recently made, Dr Christophe Guignabert will give a brief overview on some recent biological findings that have led to the identification of new promising targets in PAH and that could pave the way for future therapeutic strategies in the field.

Christophe Guignabert, PhD, is Assistant Professor at INSERM/Université Paris-Sud and Université Paris-Saclay, France. He currently leads the "Cellular and molecular basis of pulmonary endothelial dysfunction in pulmonary arterial hypertension (PAH)" team, which focuses on the aberrant pulmonary endothelial cell phenotype in PAH and on the identification of new molecular targets. His research aims to better understand the role played by endothelial cells in pulmonary vascular remodeling, on the mechanisms by which pulmonary endothelial cells interact with their environment (vascular smooth muscle cells, myofibroblasts, pericytes, and regulatory T lymphocytes) and those by which iatrogenic agents, such as drugs, contribute to endothelial dysfunction in PAH.

Dr Guignabert and his team have already highlighted several major functional alterations in the pulmonary vascular endothelium, including: (1) a transition from a quiescent state (without adhesive capacity) to an activated state with adhesive capacity; (2) an aberrant hyperproliferative and apoptosis-resistant phenotype (3) a proinflammatory phenotype characterized by an excessive release of various key cytokines and chemokines: interleukin (IL)-1 α , IL-6, IL-8, IL-12, monocyte chemotactic protein (MCP)-1; (4) an excessive production and secretion of various key growth factors including fibroblast growth factor-2 (FGF-2; basic FGF) angiotensin-II (Ang II), and leptin. The team's results have been published in J Clin Invest, Circulation, Eur Respir J, Am J Respir Crit Care Med, Am J Respir Cell Mol Biol. and Chest.

Dr Guignabert is a leading expert in in vitro techniques using human pulmonary isolated cells, and in vivo rodent models of experimental pulmonary hypertension.