Commentary

Commentary on: Xbp1s-Ddit3, DNA damage and pulmonary hypertension

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In this commentary, we discuss new observations stating that spliced X-box-binding protein 1 (Xbp1s)-DNA damage-inducible transcript 3 (Ddit3) promotes monocrotaline (MCT)-induced pulmonary hypertension (Jiang et al., Clinical Science (2021) 135(21), https://doi.org/10.1042/CS20210612). Xbp1s-Ddit3 is involved in the regulation of endoplasmic reticulum stress but is also associated with DNA damage repair machinery. Pathologic DNA damage repair mechanisms have emerged as critical determinants of pulmonary hypertension development. We discuss the potential relationship among Xbp1s-Ddit3, DNA damage, and pulmonary hypertension. Although Xbp1s-Ddit3 contributes to the regulation of cell proliferation and apoptosis and the development of vascular lesions, whether Xbp1s is a friend or foe remains controversial.

Pulmonary arterial hypertension (PAH) is a debilitating disease characterized by sustained vasoconstriction and progressive vascular remodeling of distal pulmonary arteries resulting in elevated pulmonary artery resistance and pressure, right ventricular failure, and premature death. It is recognized that pulmonary arterial smooth muscle cells (PASMCs), key actors in pulmonary vascular remodeling, exhibit a cancer-like behavior, marked by increased proliferation and resistance apoptosis. In this issue of Clinical Science, Jiang et al. reveal a novel molecular pathway involved in the etiology of pulmonary hypertension, as they demonstrated the contribution of the spliced X-box-binding protein 1 (Xbp1s)-DNA damage-inducible transcript 3 (Ddit3) axis in the development of PAH [1]. After observing an increased expression of Xbp1s and Ddit3 in the lungs of a PAH preclinical model, they showed that increased Xbp1s expression was associated with PASMCs pro-survival phenotype via Ddit3 overexpression. Finally, the authors proposed Xbp1s as a novel therapeutic target and showed that Xbp1s silencing decreased PASMCs pro-proliferative and pro-survival phenotypes, adverse pulmonary vascular lesions, and prevented the development of pulmonary hypertension in rodents. The present study further dissects the molecular mechanisms associated with pulmonary hypertension and identifies the previously unknown Xbp1s-Ddit3 axis as a novel pathological pathway involved in pulmonary vascular lesions’ genesis. Although fascinating, the present study raises numerous questions. This work was conducted on a rodent model of the disease and used hypoxia to mimic the pro-survival phenotype of PAH PASMCs. Whether Xbp1s/Ddit3 expression is increased in human PAH lungs and cells is unknown and remains to be determined, as are the molecular mechanisms underlying Xbp1s’ overexpression in pulmonary hypertension.

Xbp1s and Ddit3 are both multifactorial transcription factors involved in endoplasmic reticulum stress by regulating the unfolded protein response [2]. Xbp1s and Ddit3 expression and function are also related to DNA damage and response to DNA damage [3]. Indeed, suboptimal DNA repair may trigger endoplasmic reticulum stress. Moreover, a 2007 genome-wide study identified an association between Xbp1s and DNA damage repair mechanisms [4]. Interesting work by Tao et al. showed that, in response to DNA damage, Xbp1s is requested for efficient histone H4 deacetylation, a critical step for successful DNA repair mechanisms [5]. In cancer, Xbp1s plays a crucial role in coordinating the DNA damage response, cell proliferation, and carcinogenesis [6]. Exposition to DNA damaging agents, such as ultraviolet, radiation...
and chemical reagents, is associated with increased Ddit3 expression [7,8]. However, the precise nature of the relationship between DNA damage and the Xbp1s-Ddit3 axis in PAH remains elusive.

In the past decade, DNA damage emerged as a critical player in the development and progression of PAH [9]. Several studies demonstrated that increased DNA damage is observed in the lungs and pulmonary arteries of preclinical models of PAH and humans suffering from the disease [9,10]. In vitro, elevated DNA damage observed in PAH PASMCs and pulmonary artery endothelial cells is associated with increased cell proliferation, apoptosis resistance, and endothelial dysfunction. Beyond damage to the nuclear DNA, mitochondrial DNA also appears to be affected [9]. In addition to increased DNA damage, DNA damage repair mechanisms are also impaired in PAH. Usually, response to DNA damage engages a well-orchestrated machinery that senses the extent of DNA damage and decides of the fate of the cells and whether they will undergo repair or death. Impaired expression of critical players involved in DNA repair mechanisms has been observed in PAH [9]. Among them, the poly(ADP-ribose) polymerase-1 (PARP-1), which functions as a cellular stress sensor, was identified [11,12]. PARP-1 can modulate the fate of DNA repair, according to the intensity of its activation. Indeed, low to moderate activation of PARP-1 will permit cell survival, whereas intense PARP-1 activation will promote cell death. In PAH, increased PARP-1 expression has been associated with PASMCs pro-survival phenotype and adverse pulmonary vascular lesions [12]. The heat shock protein 90 (HSP90), a key factor in the base excision repair mechanism, is another example illustrating the close interaction between DNA damage and PAH [13]. In PAH, mitochondrial accumulation of HSP90 leads to PASMCs proliferation and pulmonary vascular remodeling.

Epigenetic modifications are implicated in both responses to DNA damage and PAH etiology [14,15]. For example, genome-wide DNA breaks are associated with enhanced acetylation of histone H4, which leads to the recruitment of the epigenetic reader bromodomain-containing protein 4 (BRD4), and the stable establishment of the DNA repair complex [16]. In response to DNA damage, increased BRD4 expression can promote cell survival by inhibiting apoptosis and stimulating hyperproliferation. Consequently, several studies demonstrated that increased BRD4 expression in PAH lungs and cells is associated with PASMCs pro-survival phenotype and pulmonary vascular remodeling [17,18]. The histone deacetylase 6 (HDAC6) is another epigenetic player involved in both DNA damage repair and PAH etiology [19]. A recent study demonstrated that increased expression of the long noncoding RNA H19 (LncRNA-H19) contributes to PAH development and correlates with the disease severity and outcome [20]. Separate work shows that LncRNA-H19 contributes to DNA damage repair and that decreased expression of LncRNA-H19 increases susceptibility to DNA damage [21].

Interestingly, artificial LncRNA-H19 overexpression also leads to Xbp1s accumulation and regulation of inflammation in epithelial cells [22]. Whether increased LncRNA-H19 expression contributes to Xbp1s overexpression in PAH remains to be investigated. Another topic for discussion is how Xbp1s expression may mitigate the effect of DNA repair-related drugs and Xbp1s, its share in the therapeutic effect mediated by these drugs in PAH remains elusive. Preclinical studies demonstrated that PARP-1 inhibitors prevent the development and progression of PAH development [12]. A PARP-1 inhibitor, olaparib, is currently being evaluated in a phase 1 clinical trial conducted in PAH (NCT03782818). Interestingly, in vitro experiments demonstrated that olaparib induced a dose-dependent increase in DNA damage and XBP1 expression, thus inducing apoptosis and decreasing the proliferation of cancer cells [23]. Similarly, BRD4 inhibitors are promising novel drugs that successfully prevent adverse pulmonary vascular remodeling and reverse pulmonary hypertension in rodents [24]. A drug named apabetalone, a BRD4 inhibitor, is currently in a phase 2 clinical trial (NCT04915300) in PAH. In cancer, chromatin immunoprecipitation experiments reveal an enrichment of BRD4 in Xbp1s gene promoter in multiple lines [25]. Consequently, BRD4 inhibitors decrease Xbp1s expression and cells proliferation and tumor growth [26]. Gamitrinib (GA mitochondrial matrix inhibitor) is a small molecule designed to target mitochondrial HSP90 [13]. In human PAH PASMCs, gamitrinib induced mitochondrial DNA damage increases apoptosis and decreases proliferation in a dose-dependent manner [13]. In vivo, gamitrinib treatment improves pulmonary vascular remodeling and hemodynamic parameters [13]. In cancer cells, gamitrinib induces increased Xbp1s expression leading to Ddit3 overexpression, which increased cell apoptosis and decreased tumor size [27]. Although evidence suggests an interaction between DNA damage-related drugs and Xbp1s, its share in the therapeutic effect mediated by these drugs in PAH remains to be elucidated.

The therapeutic effect of these drugs could potentially be associated with increased (olaparib, gamitrinib) or decreased (BRD4 inhibitors) Xbp1s expression. Confusingly, the literature suggests that Xbp1s could exert either pro-tumoral and pro-proliferative or anti-tumoral and pro-apoptotic effects. The controversial role of Xbp1s on cell proliferation merits discussion. For instance, upon silencing Xbp1s under hypoxic conditions, tumor growth and survival are decreased, which implicates Xbp1s as a key component in cell survival [28]. Conversely, Xbp1s inhibitors increased in vitro and in vivo Ewing's sarcoma cells apoptosis [29]. In the work published by Jiang et al., the inhibition of Xbp1s decreased cells proliferation and alleviated adverse pulmonary vascular remodeling in PAH [1].
Figure 1. Schematic overview of the role of the Xbp1s-Ddit3 axis in DNA damage and PAH

Xbp1s and Ddit3 promote PAH development by inducing PASMCs hyperproliferation and resistance to apoptosis. Their expression is known to contribute to the regulation of genes implicated in sustained DNA damage repair response such as PARP1, BRD4, LncRNA-H19 and HSP90, which are known to contribute to PAH development. Treatment with Olaparib (PARP1 inhibitor) and Gamitrinib (HSP90 inhibitor) is associated with an increased expression of Xbp1s. Treatment with Apabetalone (BRD4 inhibitor) is associated with a decreased expression of Xbp1s.

However, Serrano et al. showed that Xbp1s depletion is associated with increased smooth muscle proliferation and migration [30]. Moreover, conditional smooth muscle cells Xbp1s knockout increased arterial neointimal hyperplasia in a carotid artery ligation mice model [30].

In conclusion, the work from Jiang et al. increased the basic knowledge in PAH and identified Xbp1s/Ddit3 as a novel molecular axis involved in the etiology of the disease (Figure 1). This elegant study will, without a doubt, motivate future studies.

Competing Interests

The authors declare that there are no competing interests associated with the manuscript.

Abbreviations

BRD4, bromodomain-containing protein 4; Ddit3, DNA damage-inducible transcript 3; HSP90, heat shock protein 90; LncRNA-H19, long noncoding RNA H19; PAH, pulmonary arterial hypertension; PARP-1, poly(ADP-ribose) polymerase-1; PASMC, pulmonary arterial smooth muscle cell; Xbp1s, spliced X-box-binding protein 1.

References

