Silicosis

Subjects: Pathology

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programmed cell death autophagy apoptosis pyroptosis silicosis

1. Programmed Cell Death Is Necessary for Participation in the Regulatory Mechanism of Silicosis

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The current widely accepted silicosis pathogenesis is as follows: (1) Silica is identified and then phagocytosed by the alveolar macrophage (AM) via the scavenger receptor, which is the first critical defensive line for silica invasion [5][6]. Silicosis is developed through a vicious circle. AM engulfs silica to cause AM death and then releases intracellular silica that is further taken up by other AMs [7][8]; (2) Silicic acid produced by dissolved silica destroys the stability of the AM lysosomal membrane. Hydrolase released by the disrupted lysosome penetrates the cytoplasm overly and ultimately leads to AM death [9][10][11]; (3) Dead AMs can release a series of inflammatory factors, causing pulmonary inflammatory damage [12]. Correspondingly, AMs gather at the injured pulmonary tissue and stimulate fibroblasts to transform into myofibroblasts, leading to excessive deposition of the extracellular matrix and eventual silicosis fibrosis [13][14][15]. These steps are not necessarily executed in order or parallel strictly, and they are interspersed and connected to cause silicotic fibrosis.

As mentioned above, transforming growth factor-β (TGF-β) secretion stimulates fibroblasts to transform into myofibroblasts for collagen synthesis, extracellular matrix deposition, and eventual silicosis fibrosis formation [16]. The inhibited activity of autophagy has been observed in TGF-β-treated fibroblasts. MiR-449a induced autophagy activity and reduced Bcl-2 level in silica-activated fibroblasts or a silicosis mice model [17]. Meanwhile, m iR-326 also promotes autophagy activity by targeting polypyrimidine tract-binding protein 1 (PTBP1) [18]. Their over-

expression alleviated both the distribution and severity of lung lesions. HECT domain-containing protein 1 (HECTD1) is an E3 ubiquitin-protein, which has been proven to be involved in functional cellular changes in silicosis. Either circHECTD1 over-expression or HECTD1 knockdown inhibited silica-induced fibroblast activation, proliferation, and migration via regulating the autophagy activity of fibroblasts [19]. In summary, related research concerning non-coding RNA with its targeted protein, which can regulate autophagy activity, may shed new light on the therapeutic methods of silicosis. Moreover, Rho GDP-dissociation inhibitor α (RhoGDIα) knockdown inhibited collagen deposition through promoting apoptosis of myofibroblasts [20]. Overall, unlike AM, related research based on silica-activated fibroblasts or myofibroblasts should promote autophagy or apoptosis to seek promising intervention methods of silicosis. Notably, in this review, we attached much attention to related studies based on AMs and lung epithelial cells (detailed below). They are both critical targeted cells.

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3. Autophagy Is an Essential Way of Programmed Cell Death during Silicotic Progression

Silica has been proven to regulate autophagy activity via the phosphatidylinositol 3 kinase (PI3K)/protein kinase B (PKB/Akt)/mammalian target of rapamycin (mTOR) signaling pathway. Recent studies have shown that, through the utilization of mTOR inhibitor rapamycin (Rapa), autophagy alleviates silica-induced AM apoptosis [21]. Meanwhile, autophagy reduces the expression of tumor necrosis factor-α (TNF-α) and TGF-β in AMs treated with silica [22]. On the one hand, these findings suggest that the activation of AM autophagy can protect against the silica-induced excessive cell apoptosis or inflammatory response. On the other hand, an mTOR signaling pathway may be a critical point for the mechanism of autophagy. Especially, an active ingredient of the natural plant Atractylodes macrocephala Koidz, Atractylenolide III (ATL-III), accelerated the process of autophagic degradation via fostering the mTOR-dependent signaling pathway [23]. ATL-III may be the potential natural mTOR activator that has been discovered. Therefore, the development of natural or synthetic drugs targeting mTOR may be a promising method for silicosis treatment in clinical settings.

As described, the basic autophagy level has a compensatory protective function for silica invasion; however, cells seem to have the ability to sense the stress caused by silica, which further leads to dysregulation of related signaling pathways and even cell death via the abnormal occurrence of autophagy. Accumulated autophagosomes and damaged lysosomes in the AM of silicosis patients have been observed previously [24], implying that silica disrupts the normal process of AM autophagic degradation. This may be an indispensable feature of abnormal autophagy caused by excessive silica invasion. Moreover, mitophagy also participates in the mechanism of the silica-induced pulmonary toxic effect. When invading the alveoli, silica-activated AM produces mitochondria ROS (mtROS), reduces ATP contents, and breaks mitochondria function. In response to such pathological pulmonary damage, the expression of PINK and Parkin is decreased, which are regulated by BECN1. Meanwhile, the deficiency of BECN1, targeted by microRNA-1224-5p , triggered mitophagy disruption under silica circumstances [25]. Furthermore, dioscin, the main ingredient of Dioscoreaceae, eliminated damaged mitochondria via protecting impaired mitophagy against silica attack [21][26].

Intriguingly, Fe atoms were found to be accumulated on the surface of silica. Their size and number were increased with the aggravation of pathological changes of the silicosis rat model. Meanwhile, sequestosome1 (SQSTM1/p62) was accumulated around the silica while not expressed in control mice [27]. Thus, the normal silicosis animal model constructed by single-crystalline SiO 2 may not be appropriate. More attention should be

paid to the combined pulmonary toxicity by SiO 2 and its surface adsorbent. The relationship between these exogenous stimuli and autophagy in the pathological development of silicotic fibrosis should be examined deeply.

Accumulating studies seem to suggest that the change of autophagy activity fails to explain the role that autophagy plays in silica-induced pulmonary fibrosis. For instance, dioscin might delay the progression of silicosis via the activation of autophagy to eliminate damaged mitochondria [21][26]. However, enhanced autophagy activity aggravated silica-induced macrophage apoptosis in the MCPIP1 deficiency of mice. Herein, we support a hypothesis: the degree of autophagic degradation, not the change of autophagy activity, may better reflect the autophagy regulatory mechanism of certain endogenous or exogenous substances in silicotic fibrosis. Correspondingly, many natural products have attracted much attention in studies of pulmonary fibrosis [28]. They may also be protective anti-fibrotic components of silicosis by targeting autophagic degradation, such as ATL-III, dioscin, trehalose (tre, a non-reducing disaccharide), and kaempferol (kae, a flavonoid that exists in many plants and fruits) [21][29][30]. In the future, the molecular mechanism of some natural products with autophagic regulation should be taken as the starting point for exploring the interventions for silicosis.

4. Apoptosis and Pyroptosis Are Both Associated with Toxic Effects Induced by Silica

Normally, silica boosts mitochondria to produce mtROS and releases cytochrome c (cyto-c) [31][32]. Cyto-c binds apoptotic protease activating factor-1 (Apaf-1) to initiate a caspase cascade reaction: the cyto-c/Apaf-1 complex activates caspase-9 (not caspase-8) then caspase-3, and the latter can crack poly ADP-ribose polymerase (PARP), further leading to DNA fragmentation (a characteristic of cell apoptosis) [33]. In addition, the interaction between TNF receptor 1 (TNFR1) and NADPH oxidase (Phox) may reduce the mtROS production, alleviating macrophage apoptosis [34]. Our previous study had found that the decreased ratio of Bcl-2/Bax resulted in the caspase-3 activation in the silicosis mice model [35][36]. Moreover, mitochondria-mediated apoptosis occurred in mouse macrophage line MH-S cells with silica exposure, which manifested as the appearance of subdiploid cell fragments, accompanied by the activation of caspase-3 and caspase-9 [37]. The caspase-3 expression was also enhanced in LPS-intervened AMs of silicosis patients or silicosis mice lung tissue [24][38], suggesting that caspase-3 might be a critical center factor during cell apoptosis progress in silicosis. Notably, N-acetylcysteine (NAC) might alleviate the progression of silicosis via regulating the mitochondria-mediated apoptotic pathway [39].

PPP1R13B, a major member of the apoptosis-stimulating proteins of the p53 family, may perform an anti-apoptosis function through alleviating endoplasmic reticulum (ER) stress [40][41]. Moreover, a study has shown that continuous silica invasion leads to A549 cell apoptosis induced by excessive ER stress, reflected in the phosphorylation of protein kinase RNA-like endoplasmic reticulum kinase (PERK), eukaryotic initiation factor α (eIF2α), and the up-regulation of CHOP and Caspase-12. Intriguingly, N-acetyl-seryl-aspartyl-lysyl-proline (Ac-SDKP), a physiological regulatory peptide factor, may alleviate A549 cell apoptosis via the PERK/eIF2α/CHOP signaling pathway [42].

Currently, the pathological effects of the nuclear factor kappa-B (NF-κB) and TNF-α in silica-induced apoptosis remain controversial. TNF-α has been recognized as a biomarker for the early diagnosis of silicosis [43]. The

enhanced TNF-α production was observed in macrophages in response to silica activation, fostering macrophage apoptosis. Furthermore, anti-TNF-α antibodies or soluble TNF receptors improved pulmonary fibrosis in silica-exposed mice [44][45][46]. Silica was able to induce TNF-α transcription via the NF-κB activation. TNF-α also stimulated the NF-κB signaling pathway to protect the cell apoptosis against silica invasion in RAW 264.7 murine macrophages. Such a mechanism may be compensatory protection for lung tissue damage. However, excessive cell apoptosis and pulmonary inflammatory response occur with the over-activation of NF-κB [47][48]. Therefore, antagonism of TNF-α may not constitute an appropriate clinical target in silicosis. The balance between NF-κB activity and TNF-α expression may decide the degree of cell apoptosis and cell fate. Future research should consider the bidirectional role of TNF-α in silica-induced apoptosis more carefully.

However, contrary to the view above, some researchers have supported a proposal that silica alone did not activate NRLP3 inflammasome-directed pyroptosis, because IL-1β release did not change dramatically, although caspase-1 is activated in AM with a single SiO 2. Meanwhile, NLRP3 activation, subsequent ASC oligomerization, and caspase-1 activation were observed in AM with LPS priors to silica treatment. The reason may be that NLRP3 expression requires priming with microbial ligands such as LPS or endogenous cytokines, not inducing IL-1β release in unprimed macrophages. Furthermore, docosahexaenoic acid (DHA) inhibited cell pyroptosis in silica-activated AMs treated with LPS [49][50]. In summary, whether single or combined silica can induce pyroptosis in silicosis fibrosis still needs to be further explored. The significance behind this may reflect that the components of silica in an actual working environment are much more complicated than imagined.

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