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Review

# Mechanisms underlying the development of pulmonary fibrosis induced by paraquat exposure: Signaling pathways regulating the epithelial-mesenchymal transition

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## ABSTRACT

Paraquat (PQ) is a highly toxic herbicide that causes fatal pulmonary fibrosis in humans. The molecular mechanisms responsible for PQ-induced pulmonary fibrosis are still not clear, but the epithelial-mesenchymal transition (EMT) has been postulated to be one of the main mechanisms. EMT involves epithelial cell transformation into cells with mesenchymal phenotypes. A growing body of experimental evidence indicates that PQ exposure can induce phenotypes that are characteristic of EMT, including a reduction in the epithelial cell markers E-cadherin and zona occludens 1 (ZO-1), and an increase in the mesenchymal cell markers vimentin and α-smooth muscle actin (α-SMA). In this review, we summarize *in vivo* and *in vitro* studies on PQ-mediated pulmonary fibrosis, and discuss the possible involvement of signaling pathways such as transforming growth factor-β1 (TGF-β1)/Smad, Wnt/β-catenin, Notch, and hypoxia-inducible factor 1α (HIF-1α) in regulating pulmonary EMT following exposure to PQ.

**KEYWORDS:** paraquat (PQ), pulmonary fibrosis, epithelial-mesenchymal transition (EMT), signaling pathways, TGF-β1/Smad, Wnt/β-catenin, Notch, HIF-1α.

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## ABBREVIATIONS

| | | |
|---|---|---|
| α-SMA | : | α-smooth muscle actin |
| ECM | : | extracellular matrix |
| EMT | : | epithelial-mesenchymal transition |
| EMT-TFs | : | EMT-driving transcription factors |
| ERK1/2 | : | extracellular signal-regulated kinases 1/2 |
| HIF-1α | : | hypoxia-inducible factor 1α |
| LOX | : | lysyl oxidase |
| LRP | : | low-density lipoprotein receptor-related protein |
| MAPK | : | mitogen-activated protein kinase |
| MEF | : | mouse embryonic fibroblast |
| MMP | : | matrix metalloproteinase |
| mTOR | : | mechanistic target of rapamycin |
| Nrf2 | : | nuclear factor erythroid 2-related factor 2 |
| PQ | : | paraquat |
| TGF-β | : | transforming growth factor-β |
| ZEB | : | zinc finger E-box-binding homeobox |
| ZO-1 | : | zona occludens 1 |

## 1. Introduction

Paraquat (1,1'-dimethyl-4,4'-bipyridylium dichloride (PQ), also called Gramoxone and Kewuzong) is a water-soluble organic heterocyclic herbicide

that is widely used in global agriculture, especially in Asian countries [1, 2]. After accidental or intentional ingestion, PQ accumulates primarily in the lung due to the abundant polyamine transport system in the membrane of alveolar epithelial cells (types I and II) and Clara cells, and the pulmonary concentration can be 6- to 10-times higher than that in plasma [3]. Clinical respiratory manifestations of PQ intoxication include acute lung injury and acute respiratory distress syndrome, followed by progressive pulmonary fibrosis in severe cases [1, 3]. PQ induces inflammation and oxidative stress, which are considered to be responsible for the pulmonary pathology [1, 3, 4]. The toxic effects of PQ on the respiratory system are potentially lethal, and no effective medical treatments are currently available to prevent PQ-induced progressive pulmonary fibrosis [2, 3]. Therefore, it is crucial to identify the molecular mechanisms of PQ-induced pulmonary fibrosis.

Pulmonary fibrosis is characterized pathologically by excessive accumulation of extracellular matrix (ECM) and lung architecture remodeling [5]. The induction of matrix-producing myofibroblasts has a central role in the development of pulmonary fibrosis [5, 6]. One of the sources of myofibroblasts is the epithelial-mesenchymal transition (EMT) of lung alveolar epithelial cells [6, 7]. The EMT pathway enables a polarized epithelial cell to undergo multiple biochemical changes that lead to a mesenchymal cell phenotype, including enhanced cell migration and invasion, elevated resistance to apoptosis, and the production of ECM components such as fibronectin and collagen type I [7-9]. There are three types of EMTs that occur in distinct biological settings: type 1 EMT is associated with implantation, embryogenesis, and organ development; type 2 EMT is associated with tissue regeneration and organ fibrosis; and type 3 EMT is associated with cancer progression and metastasis [8]. EMT is induced by multiple signaling pathways, including growth factors/receptor tyrosine kinase, transforming growth factor-β (TGF-β), Wnt, Notch, ECM/integrins, and nuclear factor-κB (NF-κB) pathways [7, 10]. These pathways activate transcription factors that induce EMT (EMT-TFs) such as Snail, Slug, Zinc finger E-box-binding homeobox (ZEB), Twist, and β-catenin [7, 9]. Although hybrid intermediate EMT states occur during organ fibrosis [7-9, 11], EMT reduces epithelial cell markers such as E-cadherin, cytokeratin, and zona occludens 1 (ZO-1), and elevates mesenchymal cell markers such as N-cadherin, vimentin, fibroblast specific protein-1, and α-smooth muscle actin (α-SMA) [7, 8]. A growing body of experimental evidence indicates that PQ exposure can induce phenotypic characteristics of EMT and cause pulmonary fibrosis (Figure 1). In this review, we summarize *in vivo* and *in vitro* experimental studies on PQ-mediated pulmonary fibrosis, and discuss the possible involvement of signaling pathways such as TGF-β1/Smad, Wnt/β-catenin, Notch, and hypoxia-inducible factor 1α (HIF-1α) in regulating pulmonary EMT following exposure to PQ.

## 2. Signaling pathways regulating pulmonary EMT following exposure to PQ

### 2.1. TGF-β1/Smad pathway

Mammals express three TGF-β isoforms, β1, β2, and β3. TGF-β1 is most closely associated with the development of pulmonary fibrosis [12] and is considered as a master switch of EMT [13]. TGF-β activates Smad2 and Smad3 and forms complexes with Smad4, which then regulate the transcription of target genes through interactions with a variety of transcription factors such as Snail, ZEB, and basic Helix-Loop-Helix (bHLH) families [10]. Pathways that are not mediated by Smad, including RhoA (Ras homolog gene family, member A), Ras, mitogen-activated protein kinase (MAPK), phosphoinositide-3-kinase (PI3K)/Akt, Notch, and Wnt, are also linked to TGF-β-induced EMT [10, 13].

Treatment of rats with 20 mg/kg PQ increases TGF-β1 mRNA and protein levels in lung [14]. Treatment of rats with 30, 60, and 120 mg/kg PQ increases serum TGF-β1 levels and pulmonary *TGF-β1* mRNA expression [15] before the development of pulmonary fibrosis. Treatment of MRC-5 human fetal lung fibroblast cells with 100, 300, and 500 μM PQ (unknown exposure time) increases TGF-β1 production and α-SMA expression [16]. These results indicate that PQ exposure induces the expression of pulmonary TGF-β1 *in vitro* and *in vivo*.

Administration of SB431542, a specific inhibitor of TGF-β1 receptor type I/activin receptor-like kinase 5 (ALK5) that phosphorylates Smad2 and

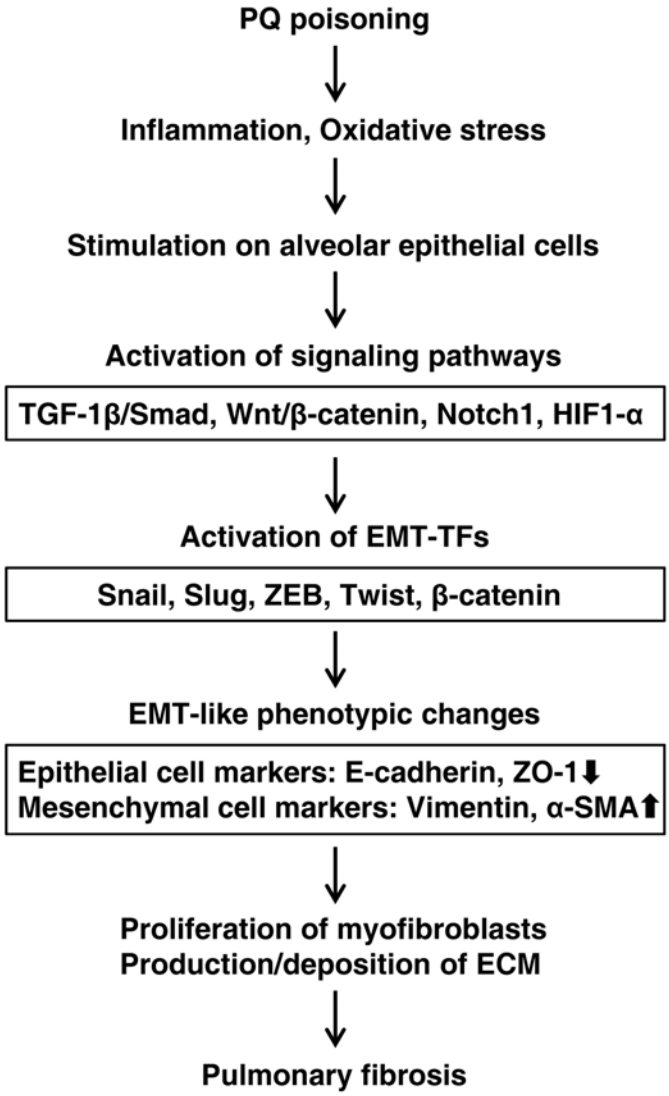


**Figure 1.** Paraquat (PQ) activates signaling pathways that regulate the epithelial-mesenchymal transition (EMT) and cause pulmonary fibrosis. EMT-TFs, EMT-driving transcription factors; ECM, extracellular matrix.

Smad3, suppresses PQ-induced spindle-shaped mesenchymal-like cell morphology, α-SMA expression, and fibronectin secretion in A549 human lung adenocarcinoma epithelial cells treated with 30 μM PQ for 12 days [17]. The same authors also found that SB431542 attenuates the mesenchymal transformation and subsequent fibrogenesis in normal human bronchial epithelial cells exposed to 30 μM PQ for 12 days [17]. Another study showed that treatment of A549 cells with SB431542 suppresses PQ-induced (20 μM for 5 days) fibroblast-like appearance, loss of epithelial cell marker (E-cadherin and ZO-1), increase in mesenchymal cell marker (α-SMA and vimentin) expression, collagen type I oversynthesis, and enhancement of migratory capacity; these effects were mediated by inhibiting Smad2 and Smad3 phosphorylation [18]. Knockdown of TGF-β1 expression *via* shRNA transfection in A549 cells suppresses PQ-induced (10 μM for 24 h) increases in TGF-β1 and Smad2 protein levels and changes the expression of mesenchymal cell marker (α-SMA and vimentin) and the E-cadherin epithelial cell marker [19]. The shRNA-mediated *in vivo* silencing of Smad3 effectively reduces procollagen type I mRNA expression and

hydroxyproline content in lung tissue of PQ-treated mice (10 mg/kg) [20]. On the other hand, treatment of rats with docosahexaenoic acid (DHA), an essential n-3 polyunsaturated fatty acid, attenuates PQ-induced (50 mg/kg) reduction of the TGF-β1 negative regulators Smad7 and SnoN, increase in *TGF-β1* mRNA expression, increase in hydroxyproline content, and collagen deposition in lung tissues [21]. These combined results clearly demonstrate that the TGF-β1/Smad pathway is involved in PQ-induced pulmonary EMT.

Treatment of mice with the tetracycline antibiotic doxycycline [22] and the Chinese medicine extract triptolide [23] have been reported to suppress PQ-induced EMT progression and subsequent pulmonary fibrosis by directly or indirectly down-regulating the TGF-β1 signaling pathway. Further studies are needed to confirm whether these chemicals are candidate therapeutic agents for preventing PQ-induced pulmonary fibrosis by targeting TGF-β1-dependent EMT progression.

### 2.2. Wnt/β-catenin pathway

Wnt signaling activation mediated by binding Wnt protein ligands to their seven-transmembrane Frizzled receptors and low-density lipoprotein receptor-related protein (LRP) coreceptors inhibits glycogen synthase kinase-3β (GSK-3β), which leads to the accumulation of cytoplasmic β-catenin (canonical Wnt signaling pathway) [10, 24, 25]. Stable, active β-catenin induces the transcription of its target gene by interacting with a nuclear binding partner, transcription factor of the T cell factor/lymphoid enhancer factor family [24]. The TGF-β1 and canonical Wnt/β-catenin pathways stimulate each other through the Smad pathway and non-Smad-mediated pathways [26]. A recent study reported that dysregulated activation of Wnt/β-catenin signaling is involved in the pathogenesis of idiopathic pulmonary fibrosis [25].

Treatment of RLE-6TN rat alveolar type II epithelial cells with 20 μM PQ for 24 h increases the mRNA and protein expression levels of β-catenin [27]. Knockdown of β-catenin expression with siRNA reverses the PQ-induced induction of EMT-like phenotypic changes and results in an increase in E-cadherin expression, a decrease in vimentin expression, and a reduction of cell invasion [27]. Treatment of A549 and MRC-5 cells with 300 μM PQ for 6 days increases the expression of Wnt1, LRP5, LRP6, and β-catenin mRNA and protein [28]. Rapamycin, an inhibitor of the mechanistic target of rapamycin (mTOR) pathway, inhibits the effects of PQ on the Wnt/β-catenin pathway, up-regulates E-cadherin mRNA and protein levels, and down-regulates α-SMA mRNA and protein levels, although the mechanism of mTOR involvement in regulating EMT is not clear [28]. Conversely, Wnt signaling activation using lithium chloride attenuates the inhibitory effects of rapamycin on PQ-induced EMT in A549 and MRC-5 cells [28]. Although *in vivo* evidence using animals is lacking, these two recent studies indicate that PQ exposure induces pulmonary EMT through the Wnt/β-catenin signaling pathway.

### 2.3. Notch1 pathway

Activation of Notch signaling requires the Notch receptors (Notch 1/2/3/4) to interact with their ligands (Jagged-1/-2 and Delta-like 1/3/4) [29]. Ligand binding leads to sequential cleavages by a disintegrin and metalloprotease (ADAM) and the γ-secretase complex in Notch. The released Notch intracellular domain (NICD) translocates to the nucleus to activate specific target genes such as the zinc finger transcription factor Snail, a repressor of E-cadherin expression [30]. Furthermore, integration of TGF-β/Smad and Jagged-1/Notch signaling pathways in EMT has been demonstrated [31].

Treatment of A549 cells with 300 μM PQ for 6 days increases Notch1 and Jagged-1 mRNA and protein expression levels [32]. Treating A549 cells with the Jagged-1 ligand reduces E-cadherin expression, increases α-SMA and Notch1 expression, and increases cell migration compared to treatment with PQ alone [32]. However, blockade of the Notch pathway with DAPT, a γ-secretase inhibitor, attenuates PQ-induced EMT-like phenotypic changes [32]. The same authors report that activation of the Notch1 pathway up-regulates the TGF-β1/Smad3 pathway in A549 cells treated with PQ [32]. Notch pathway stimulation with the Jagged-1 ligand further increases PQ-induced expression of TGF-β1, Smad3, and phosphorylated Smad3 protein,

whereas Notch pathway blockade with DAPT inhibits Jagged-1-induced expression of TGF-β1, Smad3, and phosphorylated Smad3 protein [32]. The stimulatory effects of Jagged-1 on PQ-induced EMT-like changes in A549 cells are attenuated by treatment with the TGF-β1 inhibitor SB431542 [32]. These combined results suggest that Notch signaling is involved in PQ-mediated EMT by up-regulating TGF-β1/Smad3 signaling [32]. Notch signaling promotes TGF-β1-induced EMT in A549 cells by inducing Snai1 (also known as Snail homolog 1) expression [33]. It remains to be determined whether Snail expression is up-regulated *via* the Notch pathway and whether E-cadherin expression is reduced in lung tissues after exposure to PQ. By contrast, another study showed that 50 mg/kg PQ down-regulates the expression of Notch1 mRNA and protein in mouse lung tissue [34]. Additional *in vivo* experiments are needed to confirm the role of Notch signaling in PQ-induced pulmonary EMT.

### 2.4. HIF-1α pathway

Hypoxia-induced expression of the stress-responsive transcription factor HIF-1α promotes EMT in many human malignancies [35]. Wang and colleagues reported the involvement of HIF-1α and its downstream target lysyl oxidase (LOX) in PQ-induced pulmonary EMT. Treatment of rats with 50 mg/kg PQ increases the level of HIF-1α protein in lung before the occurrence of lung hypoxia and increased TGF-β1 levels [36]. Transfection with HIF-1α siRNA reduces the levels of Snail and β-catenin expression, attenuates changes in the expression of epithelial cell marker (ZO-1) and mesenchymal cell marker (α-SMA), and reduces the fusiform shape in A549 cells exposed to 800 μM PQ for 24 h and RLE-6TN cells exposed to 160 μM PQ for 24 h [37]. Expression of LOX protein, an amine oxidase that functions in pulmonary fibrosis, is up-regulated in the lungs of rats exposed to 50 mg/kg PQ, A549 cells exposed to 800 μM PQ for 24 h, and RLE-6TN cells exposed to 80 μM PQ for 24 h [38]. Inactivation of LOX with β-aminopropionitrile suppresses PQ-induced collagen deposition in lung, spindle-shaped cell morphology, and changes in EMT-related markers including down-regulated E-cadherin and ZO-1 and up-regulated α-SMA, vimentin, and Snail, both *in vivo* and *in vitro* [38]. Silencing of LOX expression with siRNA alleviates PQ-induced EMT in A549 cells [38]. PQ-induced expression of LOX mRNA and protein declines when HIF-1α expression is silenced with siRNA in A549 and RLE-6TN cells [39]. However, the level of HIF-1α does not change when LOX is silenced [39]. These studies indicate that HIF-1α regulates PQ-induced pulmonary EMT through LOX activation. Another study proposed that microRNA-210 increases HIF-1α stability and promotes PQ-induced pulmonary EMT [40].

### 2.5. Nrf2 pathway

Nuclear factor erythroid 2-related factor 2 (Nrf2) is a transcription factor that controls the expression of antioxidant and cytoprotective genes that regulate the cellular response to oxidative and electrophilic stress [41]. Treatment with resveratrol, a natural phytoalexin, suppresses the expression of *TGF-β1* mRNA and α-SMA protein in WI38-VA13 normal human lung fibroblast cells exposed to 10 μM PQ for 24 h [42]. By contrast, resveratrol treatment of mouse embryonic fibroblast (MEF) cells derived from Nrf2 knockout mice fails to reduce PQ-induced α-SMA expression when compared to wild-type MEF cells treated with resveratrol and PQ [42]. Treatment of rats with rapamycin, an mTOR inhibitor, inhibits PQ-induced (dose unknown) pulmonary fibrosis, up-regulation of vimentin, Snail, hydroxyproline, collagen type I, and collagen type III, and down-regulation of E-cadherin and Nrf2 expression in lung tissues [43]. Sulforaphane, an activator of Nrf2, can inhibit PQ-induced changes in EMT-related markers (vimentin and E-cadherin) and Snail expression. By contrast, silencing Nrf2 with siRNA inhibits the effects of rapamycin on PQ-induced EMT [43]. These combined results suggest that resveratrol and rapamycin may protect PQ-induced pulmonary EMT by activating the Nrf2 signaling pathway, suggesting a possible role for Nrf2 in these EMT processes.

### 2.6. MAPK pathway

MAPK family members, including extracellular signal-regulated kinases 1/2 (ERK1/2), c-Jun amino-terminal kinase (JNK), and p38 MAPK, are activated in response to a variety of extracellular stimuli and involved in cell growth, differentiation, and apoptosis [44]. Treatment of RLE-6NT cells

with 100 μM PQ for 6 h induces ERK1/2 and p38 MAPK phosphorylation [45]. Inhibition of the ERK pathway with PD98059 and/or the p38 MAPK pathway with SB203580 reduces the levels of phosphorylated Smad2 protein [45]. However, the effects of the MAPK inhibitor on PQ-induced EMT-like phenotypic changes and up-regulated matrix metalloproteinase 2 (MMP-2), MMP-9, and collagen types I and III expression levels in RLE-6NT cells were not examined in this experiment [45]. Therefore, it remains to be determined whether MAPK pathway activation causes EMT in PQ-treated alveolar type II epithelial cells.

## 3. Conclusion

PQ-induced EMT and the resultant fibrotic changes have been investigated in lung tissues of rats [14, 15, 21, 36, 38, 40, 43] and mice [20, 22, 23, 34], and in cultured lung cells including MRC-5 cells [16, 28], A549 cells [17-19, 28, 32, 37-40], normal human bronchial cells [17], RLE-6TN cells [27, 37-40, 45], and WI38-VA13 cells [42], although the PQ dose and duration of exposure differ among the experiments. These *in vivo* and *in vitro* studies show that PQ induces the expression of EMT-TFs (Snail and β-catenin) and EMT-like phenotypic changes including the reduction in epithelial cell marker (E-cadherin and ZO-1) expression, the increase in mesenchymal cell marker (vimentin and α-SMA) expression, the synthesis of ECM components (fibronectin, collagen types I/III, and hydroxyproline), increased MMP-2 and MMP-9 expression, enhanced cell migration and invasion, and the spindle-shaped morphology of cells. PQ-induced pulmonary EMT appears to be dependent on several signaling pathways, including the TGF-β1/Smad pathway [14-23], the Wnt/β-catenin pathway [27, 28], the Notch1 pathway [32], the HIF-1α pathway [36-40], and the Nrf2 pathway [42, 43] (Figure 1). The crosstalk between TGF-β (both Smad-mediated and non-Smad-mediated pathways) and Wnt pathways, TGF-β and Notch pathways, and Notch and HIF-1α pathways may regulate the signaling pathways leading to EMT in lung cells after exposure to PQ. It has been reported that PQ-induced expression of cytokine interleukin 6 (IL-6) in macrophages has a role in pulmonary fibrosis by enhancing EMT process [46]. Future work will investigate the mechanism, activation, and transduction of signaling pathways responsible for EMT induced by PQ. These data will provide evidence for the molecular mechansims of PQ-induced pulmonary fibrosis, and potentially identify therapeutic targets for pharmacological research.

## CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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