Caveola is a key vehicle for paraquat uptake into lung

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Abstract Paraquat dichloride (PQ) is an effective and widely used herbicide for eliminating weeds. However, once being accidentally or voluntarily ingested, PQ-poisoned patients have the very high incidence of adult respiratory distress syndrome because lung can actively absorb PQ. Since the 1970s, evidence suggested that polyamine competitively inhibited uptake of PQ into lung tissue; therefore, polyamine transport system has been regarded as an important vehicle for PQ uptake into lung. However, so far, we cannot clone or detect the polyamine transport system in mammalian animal. Recent evidence from diverse sources has suggested that caveola may be an important vehicle for polyamine absorption into lung. Herein we hypothesise that caveola is a key vehicle for PQ uptake in lung and hence blocking the expression of caveola may serve as new targets for treatment of PQ poisoning.

Introduction
Paraquat (N,N-dimethyl-4,4-bipiridinium, PQ) is a potent herbicide which was widely used in more than 130 countries. Since its introduction in agriculture in 1962, thousands of deaths each year are due to accidental or intentional ingestion of PQ [1]. The lung is the main target organ for toxicity of PQ [2]. A larger dose of PQ (more than 30 mg kg \(^{-1}\) in humans) rapidly leads to death from serious pulmonary damage such as haemorrhage, oedema and infiltration of inflammatory cells into the lung tissue [3]. Smaller doses of PQ (less than 16 mg kg \(^{-1}\)) may induce proliferative pulmonary fibrosis after several days [4].

PQ is especially toxic to the lung, mainly because of its selectively active uptake by lung cells and localised redox cycling in the alveolar epithelium [5]. Alveolar cell types I, II and Clara cells are main targets because they can actively absorb PQ [6,7]. Lock et al. [8] found that endogenous amines competitively inhibited PQ accumulation in rat lung slices. From then on, it is commonly believed that lung actively takes up PQ via the polyamine transport system. However, so far, in mammalian cells, no polyamine transport system has been

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found or cloned [9]. Therefore, we must suspect whether or not lung tissue has polyamine transport system involved in PQ absorption.

Caveolae prominently located in alveolar cell types I, II and Clara cells [10,11]. They have been implicated in signal transduction and endocytosis such as albumin during acute lung injury [12,13]. PQ also binds serum haemoglobin and albumin after oral ingestion [14,15]. Moreover, polyamine, the competitive inhibitor of PQ, was absorbed via caveola-dependent endocytosis in colon-cancer-derived cells and gastrointestinal tissues [16,17]. Does caveola also play an important role during PQ penetration into lung?

**Hypothesis**

Alveolar cell types I, II and Clara cells are main targets of PQ because they can actively uptake PQ. Meanwhile, these cells most prominently express caveola. Polyamine, the competitive PQ uptake inhibitor, was transported by caveola-dependent endocytosis in colon-cancer-derived cells and gastrointestinal tissues. The fact of albumin-binding PQ also adds the possibility that caveola may mediate PQ absorption into lung tissue. Based on these findings, we speculate that caveola is a key vehicle for PQ uptake in lung tissue, and hence blocking the expression of caveola may serve as new targets for the treatment of PQ poisoning.

**Testing the hypothesis**

This hypothesis could be tested by following strategies. In PQ-poisoned animal model, we can use methyl-β-cyclodextrin (dextrin) to deplete caveola, caveolin-1 siRNA or caveolin-1 phosphorylation inhibitor (e.g., Src inhibitor) to show the role of caveola on PQ penetration into lung. With caveolin-1 small interfering RNA (siRNA) or caveolin-1 knockout mice model, we can inversely investigate whether caveola plays an important role on PQ uptake into lung. Furthermore, we can test the possibility that the inhibition of caveolar endocytosis can attenuate the PQ-induced acute lung injury through evaluating associated indexes (e.g., wet/dry ratio, lactate dehydrogenase and myeloperoxidase).

**Potential clinical implications**

It is beneficial to treat PQ-induced acute lung injury through decreasing the lung PQ concentration. To prevent the accumulation of PQ in lung tissue, many substances such as polyamine, n-propranolol, imipramine, chlorpromazine and PQ-specific antibody have been tested and got disappointing results.[2] For example, spermidine and putresine are unable to decrease either PQ accumulation in the lung or its toxic effect on PQ-induced acute lung injury in rats.[18,19] Therefore, it is very urgent to produce new drugs to inhibit PQ absorption. If our hypothesis were proved correct, we would be able to get a new treatment for PQ-poisoned patients.

**Conflict of interest**

The authors have no conflict of interest.

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**References**


