Modeling acute silica-induced inflammation using precision-cut lung slices

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Introduction. Silicosis is an occupational lung disease caused by the inhalation of respirable crystalline silica, characterized by chronic inflammation and progressive massive fibrosis. Current *in vivo* and *in vitro* models present limitations in replicating the pathophysiological features of silicosis, hindering the development of effective therapies.
Aims. To establish a novel *ex vivo* model to investigate acute inflammatory responses in both mouse (mPCLS) and human (hPCLS) precision-cut lung slices exposed to different types of commercial silica.
Methods. PCLS from male C57BL/6 mice (n=5) and human lung tissue resections (n=5) were untreated (control) or treated with silica (Min-U-Sil 5, NIST 1878b or quarry-derived DQ12) at 200 or 400 μg/mL, in the absence or presence of lipopolysaccharide (LPS; 10ng/mL) for 5 days. PCLS viability (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay; MTT) and silica-induced cytotoxicity (lactate dehydrogenase assay; LDH) were assessed. Silica uptake was determined via polarized light microscopy, and secretion of cytokines (TNFα, IL-6, IL-1β, IL-10, TGF-β) and procollagen were quantified by ELISA of PCLS conditioned media. Collagen deposition (Masson's trichrome), macrophage number (F4/80), and α-SMA expression were assessed in fixed histological sections of PCLS.
Results. Viability of mPCLS and hPCLS was preserved with all silica treatments, but high cytotoxicity was observed with DQ12 and NIST 1878b silica (mPCLS). Macrophage uptake of Min-U-Sil 5, NIST 1878b, and DQ12 was confirmed in both mPCLS and hPCLS, with cell aggregation around silica particles and evidence of activated and foamy macrophages, apoptotic bodies, and macrophage disintegration visualised by histology in mPCLS. Silica-induced cytokine secretion of IL-1β, TNF-α, and IL-10 was highest in DQ12-treated hPCLS co-stimulated with LPS. Despite modest increases in procollagen secretion, there was no collagen deposition or increased α-SMA expression in silica-treated mPCLS regardless of LPS, at the 5-day endpoint.
Discussion. Silica treatment of PCLS effectively induced acute inflammation, recapitulating aspects of the initiation of silicosis, but without establishing fibrosis. This model could be utilised to compare the damaging effects of exposure to different types of silica, study mechanisms driving early silicosis, and screen novel therapeutics.