Revisiting the paradigm of silica pathogenicity: silanols, not crystallinity, as key determinant

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Exposure to respirable silica dusts is associated to severe lung diseases, including silicosis and lung cancer, and is still a current source of concern for the heath of many workers and those using silica in nanotechnologies. Crystallinity has always been considered as the main feature of hazardous silica dusts. However, crystalline silicas are not all equally pathogenic, and some still unidentified physico-chemical differences between particles account for the variability of the silica hazard.

We recently synthesized a set of quartz crystals of respirable size, exposing as-grown, intact crystal faces. These particles showed a very low biological activity in a series of cellular tests relevant for the pathogenicity of quartz, indicating that the activity of quartz dust is not necessarily contingent to crystallinity. Mechanical grinding of these quartz crystals markedly increased their activity. By combining this finding with studies on a large set of both amorphous and crystalline silica particles, the surface spatial/energetic configuration of silanols emerged as a relevant characteristic accounting for damage to cellular membranes. We also correlated the ability of quartz particles to cause membranolysis with their capacity to activate the enzymatic machinery inflammasome and trigger a pro-inflammatory response, a step at the origin of silicosis and lung cancer. Our current hypothesis is that characterizing silanols through physico-chemical and *in vitro* analyses allows identifying the pathogenic activity of silica materials.

We are currently validating our hypothesis *in vivo* and developing a set of assays to identify and predict the respiratory hazard of silica particles based on the analysis of their surface silanol distribution. The results obtained on a panel of model quartz samples prepared *ad hoc* (i.e. particles with defined and designed physico-chemical properties) showed significant differences in their membranolytic and cytotoxic activity consistent with the hypothesis, confirming the relevance of silanols. Preliminary analyses via diffuse reflectance infrared spectroscopy (DRIFTS) indicated that this technique is promising to clearly reveal the silanol distribution of the silica particles.

Keywords silica, quartz, silanol, membranolysis, inflammasome