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Letter to the Editor

Sharing different perspectives to understand asbestos-induced carcinogenesis: A comment to Jiang *et al.* (2016)

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Dear Editor,

This letter reports some constructive observations on the recent findings by Jiang *et al.* (2016) that have inspired a more general comment on how the research on asbestos should take advantage of the different existing multidisciplinary perspectives so to flow into a final comprehensive model of asbestos-induced carcinogenesis.

The widespread use of asbestos minerals has exposed both workers and the general population to asbestos-induced lung diseases to such an extent that the asbestos pandemia is a global concern today. The efforts of different research groups worldwide are targeted at understanding the extremely complex biochemical reactions at the basis of the toxicity and pathogenicity of mineral fibers, to find proper medical treatments and prevention strategies of such malignancies. In this scenario, the contributions by Jiang *et al.*[1,2] are focused on the pivotal role of iron in asbestos-induced carcinogenesis, indicating that local iron overload in UICC chrysotile and crocidolite is a major cause of pathogenesis. These authors claim that iron elimination from the mesothelial environment (e.g. by oral administration of deferasirox) can confer dual merits for preventing asbestos-induced mesothelial carcinogenesis by simultaneously suppressing inflammation and mesothelial proliferation.

The key role of iron in inducing fiber toxicity and pathogeneicity has been known for a long time.[3] Specifically, Fe^{2+} associated with asbestos promotes the formation of highly reactive HO· species through a Fenton-like chain reaction.[4] Recently, specific studies on UICC chrysotile and crocidolite[5] reported that the potential to release HO· species also depends upon the dissolution time of the fibers determining surface iron availability, with chrysotile showing much shorter dissolution time than amphiboles both *in vitro* and *in vivo* and, hence, comparable release of iron in the same time span.[6,7]

The report by Jiang *et al.*[2] is a good example of the general problem that afflicts the preponderance of publications from our "asbestos scientific community": the lack of a multidisciplinary character and the unilateral perspective of the scientific imprint (pathology in this specific case). It is a good piece of work that lacks a basic general model and that has not been put into the context of the existing literature data. The declared mission of the authors "to elucidate the carcinogenesis mechanism of asbestos-induced malignant mesothelioma to discover clues for malignant mesothelioma prevention"[2] requires more than a single vision. The creation of a comprehensive model explaining at a molecular scale the complex mechanisms of carcinogenesis can only be obtained at the intersection of different perspectives and by the comparison of experimental evidence from other research fields (e.g. biochemistry, mineralogy, physics, and toxicology) to take into account the complex synergy of all the factors at play in defining the toxicity and pathogenicity of mineral fibers (e.g. fiber morphometry, frustrated phagocytosis, production of reactive oxygen species/nitric oxide synthase, inflammasome models, genetic factors, and many more; see, for example, Manning *et al.*[8]).

The recognition of the anticarcinogenic therapy proposed by Jiang *et al.*[2] would benefit from the clarification of a number of issues of paramount importance that are apparently underestimated in the paper: (i) a model explaining at a molecular scale the biochemical reactions leading to iron overload and in turn inflammation and proliferation processes is needed; (ii) because the origin of iron overload in the body of humans/mice in the presence of asbestos fibers is still controversial,[9] it is debatable to assume that local iron overload is only due to uptake from the extracellular compartment and to rule out the role of fiber structural iron; (iii) because the so-called "asbestos bodies" formed after iron accumulation around asbestos fibers are considered by a part of the scientific community as a mechanism of defense and not a threat,[9] it is too superficial to consider iron accumulation just as a factor of toxicity inducing carcinogenesis; (iv) does iron overload concentrate active Fe^{2+} or Fe^{3+}? This makes a huge difference in defining the role of iron in the production of toxic reactive species; (v) mesothelial cells have been used in the study but pleural macrophages and phagocytosis must also be considered in a general comprehensive model; (vi) because there is still controversy in the literature[10] regarding the global ban of chrysotile, the conclusion that "chrysotile is apparently a carcinogen stronger than crocidolite and its effects on lung carcinogenesis require immediate re-evaluation"[2] requires further experimental evidence.

These comments should be taken in a constructive way and as general inspiration for future research lines redirected toward a multidisciplinary action, involving different perspectives such as biochemistry, mineralogy, crystallography, toxicology, and others. Sharing different perspectives and working in synergy with a multidisciplinary view is not just a need, but

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the awareness that it is the only key to disclosing the very mechanisms of asbestos-induced carcinogenesis.

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Disclosure Statement

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