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Letter to the Editor

In response to Sharing different perspectives to understand asbestos-induced carcinogenesis: A comment to Jiang *et al.* (2016) by Alessandro Francesco Gualtieri (2017)

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Dear Editor,

This letter responds to the commentary[1] on our paper.[2] We would like to thank Dr Alessandro Francesco Gualtieri for his interest in our paper and for his many constructive comments. We agree with the idea that asbestos-induced carcinogenesis requires a multidisciplinary perspective, including biochemistry, mineralogy, physics and toxicology, as he described.

As pathologists, we recognize that giving intraperitoneal UICC chrysotile, crocidolite and amosite generates malignant mesothelioma in almost 100% of rats *in vivo*,[3] whereas giving other fibrous materials does not.[4] We would like to answer some of the questions raised by Dr Gualtieri.[1] (i) Because mesothelial cells are the targets of mesothelioma carcinogenesis, the proposed model is reasonable, but abundant adipocytes in the peritoneal cavity promote carcinogenesis in collaboration with macrophages and this model disregards the travelling of asbestos fibers from the airway to the somatic cavity, which, indeed, requires decades in humans. (ii) The origin of iron is an interesting issue. We suggested the importance of hemolysis and the adsorption thereafter of hemoglobin on asbestos fibers in the lung.[5] Alternatively, the recent cutting-edge mineralogical studies by Dr Gualtieri clearly showed the components/localization of iron on asbestos[1] and are of much interest for further consideration. (iii) Asbestos bodies are representatives of corpses of macrophages, indicating that numerous thin and long asbestos fibers presumably passed through the lung parenchyma. Our data demonstrated the high affinity of hemoglobin to asbestos, forming a niche for oxidative reactions.[5] (iv) We believe that catalytic Fe(II) is more important than Fe(III) in carcinogenesis because it initiates a Fenton reaction, whereas Fe(III) is almost insoluble at neutral pH. Fluorescent visualization of catalytic Fe(II) is currently available.[6] (v) We did not emphasize the two different roles of macrophages:[2] scavenging foreign fibers and promoting inflammation where thin and long fibres cannot be transported to lymph nodes. The inflammatory response after intraperitoneal injection is indeed proportionally associated with mesothelial carcinogenesis and important.[7] (vi) Although there may be some controversy about banning chrysotile (white asbestos with threshold and impurity issues) globally, chrysotile is carcinogenic to mesothelial cells (IARC Group 1) and should be banned as soon as possible.[8] The important point is that asbestos-induced mesothelial carcinogenesis takes a few decades. Cancer becomes the predominant public health problem after a country has conquered the major infectious diseases and achieved a longer average lifetime of the population. Cancer prevention in this way is important for the future of every country.

We believe that local iron overload is the major mechanism of pathogenesis in asbestos-induced mesothelial carcinogenesis, based on the genetic alterations in malignant mesothelioma induced by asbestos[3] in comparison to an iron-induced cancer rat model,[9] the observation of local iron deposition, and the preventive effects of iron chelators.[10] However, we currently think that neither desferal nor deferasirox is practically applicable to people who have already been substantially exposed to asbestos because of the invasive nature of administration (intrapleural injection) of desferal[2] and the potential renal side-effects of deferasirox. Regular blood donation or phlebotomy could be the best strategy for the prevention of asbestos-induced carcinogenesis, if it is experimentally demonstrated to be effective.

We would like to encourage epidemiologists worldwide to collect data on the role of iron in carcinogenesis, including lung cancer associated with asbestos exposure. Iron is the most fundamental metal in our body and there is no way to excrete excess iron after it has been taken up into the blood, except by hemorrhage. The reaction to a foreign body is inflammation, similar to that to bacteria. To avoid feeding iron to bacteria, our cells execute mechanisms to decrease extracellular iron levels, which eventually lead to intracellular excess iron. This is another mechanism of local iron overload. Therefore, anti-inflammatory measures would work as well. We further believe that asbestos may even have been associated with the origin of life on Earth. Thus, any scientific and constructive collaborative efforts, as well as discussion, are welcome.

Disclosure Statement

The authors have no conflicts of interest.

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References

1 Gualtieri AF. Sharing different perspectives to understand asbestos-induced carcinogenesis: A comment to Jiang *et al*. (2016). *Cancer Sci* 2017; **108**: 156–7.
2 Jiang L, Chew SH, Nakamura K, Ohara Y, Akatsuka S, Toyokuni S. Dual preventive benefits of iron elimination by desferal in asbestos-induced mesothelial carcinogenesis. *Cancer Sci* 2016; **107**: 908–15.
3 Jiang L, Akatsuka S, Nagai H *et al.* Iron overload signature in chrysotile-induced malignant mesothelioma. *J Pathol* 2012; **228**: 366–77.
4 Nagai H, Okazaki Y, Chew SH *et al.* Intraperitoneal administration of tangled multiwalled carbon nanotubes of 15 nm in diameter does not induce mesothelial carcinogenesis in rats. *Pathol Int* 2013; **63**: 457–62.
5 Nagai H, Ishihara T, Lee WH *et al.* Asbestos surface provides a niche for oxidative modification. *Cancer Sci* 2011; **102**: 2118–25.
6 Wang Y, Okazaki Y, Shi L *et al.* Role of hemoglobin and transferrin in multi-wall carbon nanotube-induced mesothelial injury and carcinogenesis. *Cancer Sci* 2016; **107**: 250–7.
7 Nagai H, Okazaki Y, Chew S *et al.* Diameter of multi-walled carbon nanotubes is a critical factor in mesothelial injury and subsequent carcinogenesis. *Proc Natl Acad Sci USA* 2011; **108**: E1330–8.
8 Editorials this week: Asbestos scandal. *Nature* 2010; **468**: 868.
9 Akatsuka S, Yamashita Y, Ohara H *et al.* Fenton reaction induced cancer in wild type rats recapitulates genomic alterations observed in human cancer. *PLoS ONE* 2012; **7**: e43403.
10 Nagai H, Okazaki Y, Chew SH, Misawa N, Yasui H, Toyokuni S. Deferasirox induces mesenchymal-epithelial transition in crocidolite-induced mesothelial carcinogenesis in rats. *Cancer Prev Res* 2013; **6**: 1222–30.