

Figure S1. Pleural fibrosis. Mesothelioma cells invading the reactive pleural fibrosis. DAB solution was used to stain  $\alpha$ SMA, and HistoGreen was used to stain AE1/AE3. Mesothelioma cells were positive for AE1/AE3 (arrows). Fibrosis and  $\alpha$ SMA<sup>+</sup> CAFs were observed even in some regions without mesothelioma cells. Such fibrosis may exist before carcinogenesis. All images are shown at the same magnification.  $\alpha$ SMA,  $\alpha$ -smooth muscle actin; CAFs, cancer-associated fibroblasts; H&E, hematoxylin and eosin; DAB, 3,3'-diaminobenzidine.

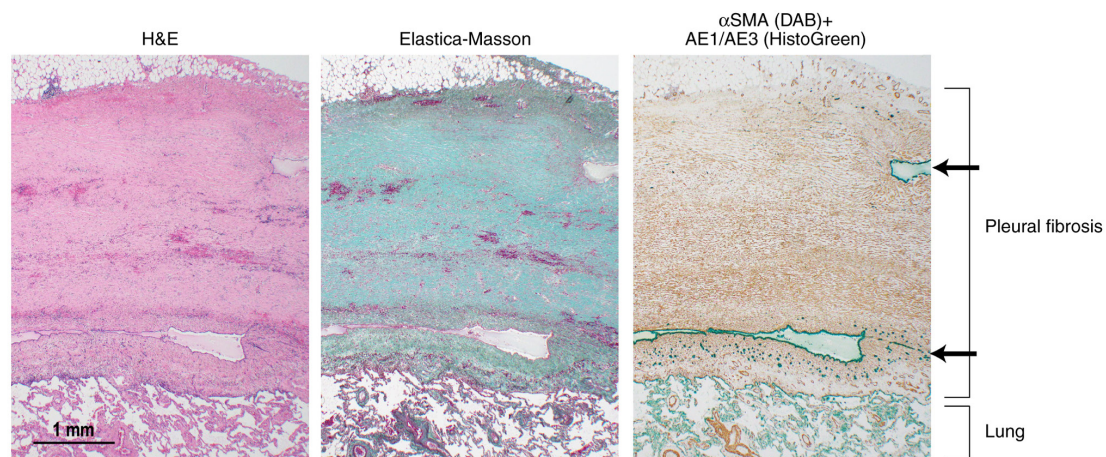


Figure S2. Distinction between mesothelioma cells and CAFs. Epithelioid mesothelioma is defined as a tumor composed of more than 90% of epithelioid components (sarcomatoid components <10%), while sarcomatoid mesothelioma is defined as a tumor composed of more than 90% of sarcomatoid components (epithelioid components <10%). Note that the epithelioid components consist of polygonal, oval, or cuboidal tumor cells, whereas the sarcomatoid components consist of elongated and spindled tumor cells with considerable mitotic activity and pleomorphism. The term sarcomatoid is defined by the cytologic morphology of tumor cells that are similar to those cells found in soft tissue sarcoma such as fibrosarcoma and leiomyosarcoma. (Top panels) Epithelioid components and CAFs. Epithelioid mesothelioma cells had a larger rounded nucleus than CAFs and nuclear atypia (arrows) and were positive for AE1/AE3. CAFs had an elongated cytoplasm and a spindle-shaped nucleus without atypia and were negative for AE1/AE3. (Bottom panels) Sarcomatoid components in epithelioid mesothelioma and CAFs. Although some of the epithelioid mesothelioma adopted a spindle shape (sarcomatoid components; arrow heads), they were positive for AE1/AE3. This case was defined as epithelioid mesothelioma because the tumor was composed of more than 90% of epithelioid components. CAFs, cancer-associated fibroblasts; CTGF, connective tissue growth factor; H&E, hematoxylin and eosin; DAB, 3,3'-diaminobenzidine.

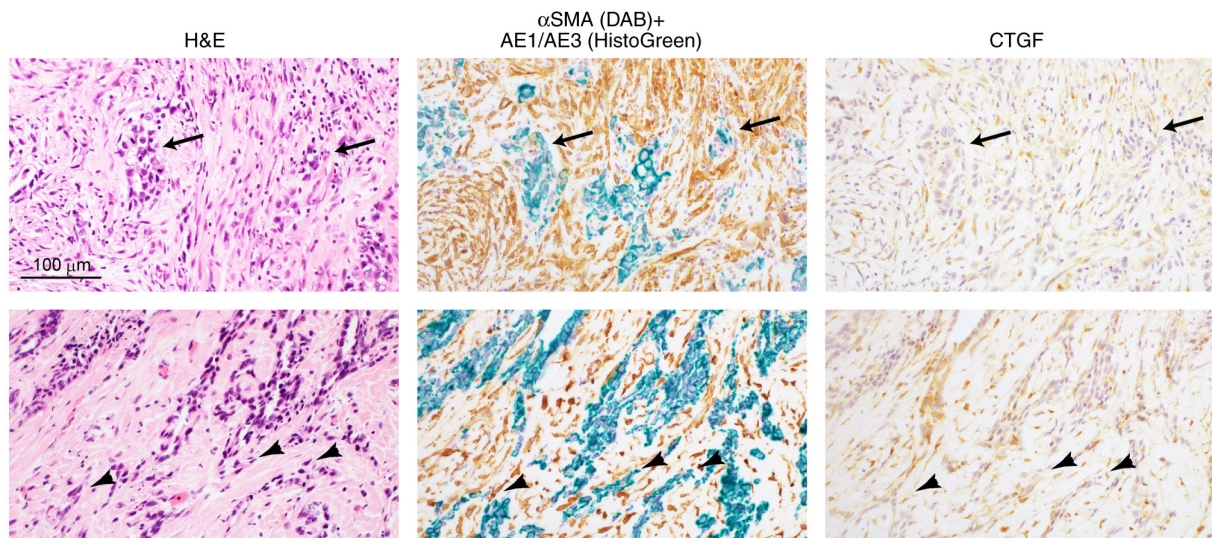


Figure S3. CTGF and Meflin in mesothelial cells. Mesothelial cells (arrows) covered the pleural cavity and were positive for AE1/AE3 and negative for CTGF and Meflin. All images are shown at the same magnification. CTGF, connective tissue growth factor; H&E, hematoxylin and eosin; DAB, 3,3'-diaminobenzidine; Meflin, mesenchymal stromal cell- and fibroblast-expressing Linx paralogue.

