Osteopontin (secreted phosphoprotein 1; SPP1) has been identified in human lung cancer and has been linked with enhanced tumour progression. To examine its functional role, we induced lung tumours by repetitive urethane or MCA/BHT lung carcinogens in C57BL/6 mice lacking both (Spp1-/-), one (Spp1 +/-), or no (Spp1+/+) copy of the endogenous Spp1 gene. Primary end-points were lung tumour number and size; secondary end-points were SPP1 expression, epithelial cell survival, carcinogen-induced inflammation, and angiogenesis. Data are presented as mean ± SD.

Compared with Spp1+/+ mice (n = 22), Spp1-/- mice (n = 25) developed dramatically fewer and significantly smaller lung tumours in response to urethane, while Spp1± mice (n = 12) behaved similar to Spp1-/- mice (number/diameter of lung tumours in Spp1+/+, Spp1 +/-, and Spp1-/- mice, respectively: 16.1 ± 12.7/1.2 ± 0.3 mm, 2.4 ± 2.3/0.9 ± 0.2 mm, and 1.3 ± 1.6/0.7 ± 0.2 mm; P < 0.05 for comparison of Spp1+/+ with Spp1-/- and Spp1+/+ mice). Spp1-/- mice were also protected from two-hit MCA/BHT-oncogenesis compared with Spp1+/+ controls. Spp1-/- mice displayed decreased epithelial cell survival and reduced numbers of airspace macrophages early after urethane, and enhanced tumour cell apoptosis and limited tumour angiogenesis at late stages of lung tumour progression. SPP1 was expressed in the naïve lung by non-ciliated airway epithelial cells and alveolar macrophages and was significantly up-regulated during multi-stage lung carcinogenesis.

Our data indicate that SPP1 is functionally involved in airway epithelial carcinogenesis and may present a target for lung cancer treatment and prevention.