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2. Title
   Role of Nicotine-induced Sympathetic Nervous Innervation in Lung Metastasis

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4. Summary
   A role of the sympathetic nervous system remains unclear in pre-metastatic environments. Therefore, we investigated the function in pre-metastatic lungs by using chemical sympathectomized tumor-bearing mice. Recruitment of myeloid-derived suppressor cells was significantly reduced, and S100A8 expression was attenuated in sympathectomized tumor-bearing mouse lungs compared with those of control tumor-bearing mice. Moreover, lung metastasis was markedly decreased in sympathectomized mice. We also found that neuro-immune cell interactions in pre-metastatic lungs that was rarely observed in healthy lungs, and CD11b-positive immune cells were stimulated with noradrenaline released from terminal ends of sympathetic nerve terminals mediated by the β2 adrenaline receptor *in vitro*. We searched for neuron-related molecules that modulate nerve fiber projections in pre-metastatic lungs and discovered non-integrated nerve fiber projections in *Sema3a* knockout mouse lungs. Taken together, Sema3A might function as a guardian that prevent sympathetic nerve fibers from invading to lung parenchyma and interacting with immune cells.