Uncovering novel cancer therapeutics using the Exoneural Medicines Platform: The role of innervation in cancer

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Inhouse Tissue clearing and imaging pipeline

Abstract

Peripheral nerves were first described as a component of tumors in the late 19th century. In the mid 20th century early preclinical studies indicated that tumor cells could recruit innervation from spinal cord ganglia and that stresses promoted tumorgenesis.

Within the last 10 years improvements in technologies allowing neuronal tracking and regulation of neuronal function have uncovered a role for both autonomic and sensory innervation in multiple tumor types. Initial studies have implicated this biology in prostate, pancreatic, gastric and breast cancer, among others and point to a role for nerves in initiation, maintenance and metastasis of tumors. The stimulation of tumor cell growth by neuronal growth factors, the recruitment of neurites by tumor cells, the invasion and migration of tumor cells along nerves (perineural invasion), and the role of innervation in driving tumor angiogenesis are just a few examples of how peripheral nerves interact with the tumor microenvironment.

Indeed, an argument could be made that innervation of tumors should be considered a hallmark of cancer.

We describe here a biological platform that can define and decode the role of neural signaling in cancer. This platform, which we call Exoneural Medicines Platform™, has 6 technical components: 1) in vitro coculture models of primary neurites with both tumor and immune cells, 2) advanced imaging models to define the neural component of tumors, 3) AAV and transgenic tools that allow regulation of neurons proximal to tumors in vivo and in vitro, 4) neural-focused functional genomics, 5) neural-focused bioinformatics, and 6) a focused functional genomics with sgRNAs targeting neuronal genes, transporters and ion channels: ~11,000 sgRNAs targeting ~1800 genes, 6 sgRNAs per gene.

Tumor innervation revealed by CLARITY

CRISPR screening using highly innervated models

Explant culture

In vitro coculture of primary neurites with both tumor and immune cells

Neuroma-nipulation

We can retrogradely label the tumor-experiencing neurons by either ablating the neurons or sectioning the nerve, and present our results in vitro.

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Neuron Cancer cells

Compartmentalized chamber

We can reproducibly label the cancer innervating neurons by ablating all DRG cells and present our results in vitro.

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