Immunogenicity of substance P

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Introduction
Substance P (SP) has been widely recognized roles in pain perception, vasodilation, and itching. When eating peppers, for example, it is the triggered release of SP that causes the sensation of burning. In response to an assumed injury, the body promotes a damage response with vasodilation and the recruitment of CD29(+) stromal-like cells. Our research is investigating an additional role: the promotion of an immunogenic response.

Background
A cerebral spinal fluid (CSF) bank was screened using triple quadrupole mass spectrometry to identify proteins that were positively or negatively correlated with cancer progression and metastasis. One protein that stood was Substance P. Melanoma patients with low levels of SP tended to have shorter periods between diagnosis of melanoma and metastasis to the brain. On the other hand, patients with higher SP tended to, on average, have longer periods between diagnosis and brain metastasis. (Figure 1).

Hypothesis & Design
Extensive reviews of literature for “Substance P,” and “cancer,” reveals little that explain this clinical observance. Several studies suggest that SP is actually a promotor of cancer proliferation, by activation of the ERK pathway. These studies suggest that elevated SP promotes the growth and eventual metastasis of melanoma, the opposite of our observations (Figure 1).

One alternative explanation is that, rather having a direct effect on the tumor, SP acts as an immune modulator. Instead of directly influencing the tumor microenvironment, SP might prime the adaptive immune system towards a Th1, anti-tumor response. This possibility has been reinforced by a study showing that SP-treated dendritic cells home to lymph nodes and produce interleukin-12, biasing the immune system towards a Th1 response. (Figure 2) A Th1 response in patients may account for the apparent differences in metastasis time between high and low SP patients.

Outcomes
The ability of SP to effectively hinder metastasis and tumor growth by an immunogenic response will be determined by several standards: a diminished growth of flank tumors, a decrease in the number of metastases to the lung, and an increased recruitment of anti-tumoral primed cells to the location of tumors. Flank tumor growth will be determined by calipers. Lung metastases will be determined by counting (Figure 3). The immune response will be determined by IHC and FACS (Figures 4 and 5). Cumulatively, these experiments will attempt to mirror the results seen in patient CSF, and identify a likely mechanism.

Reflection
During my time on co-op I was fortunate to learn a great deal in my field of interest: neuro- oncology. I saw the growth and research of new treatment options, like NovoTTF and mTMZ. Additionally, I was given room to research an NIH funded project, design an experimental approach based upon existing literature, and receive IACUC approval for experimentation. I am now carrying out the experiments outlined by this poster. In other projects I have investigated the activation of NK cells, performed data analysis on a Phase 1 metronomic temodar trial, and facilitated in the screening of a CSF bank for biomarkers. The experiences gained have given me enormous insight and clarified my career outlook.

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