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Therapeutic Agents Targeting Tumor Associated Macrophages in Obesity

Overweight and obesity are linked to an increased risk and worsened outcome from many cancers, including colorectal, pancreatic and breast cancer, but the mechanisms responsible for these phenomena are unknown.

Inventors in Stanford's Engleman lab discovered that these types of tumors grow faster in mice rendered obese through a high fat diet. Because macrophages play an important role in diseases associated with obesity and are present in high frequency in tumors, tumor-associated macrophages (TAMs) may contribute to this accelerated tumor growth. TAMs in tumors implanted into obese mice promote tumor growth, since their depletion from these mice results in slower tumor growth. TAMs in the tumors of obese mice express high levels of molecules that blunt immune activation of macrophages (in contrast to macrophages in obese mice that are outside of tumors), and obese mice in which the genes encoding these molecules are absent do not display accelerated tumor growth.

Agents that neutralize or inhibit the functions of these molecules are expected to have therapeutic activity against tumors in the setting of obesity, including monoclonal antibodies, small molecules, and genetic approaches including RNAi that can knock down the expression of these molecules. Conversely, since these molecules inhibit macrophage-mediated immune inflammation, agents that enhance the signaling of these molecules may prove useful in the treatment of autoimmune and inflammatory diseases.

Stage of Development
In Vivo Research

Applications

- Cancer treatment in obese and overweight persons

Advantages

- Sole cancer treatment targeting obese and overweight populations, which suffer impaired outcomes

Publications

- Bagchi, S., Yuan, R., Huang, H. L., Zhang, W., Chiu, D. K. C., Kim, H., ... & Engleman, E. G. (2024). The acid-sensing receptor GPR65 on tumor macrophages drives tumor growth in obesity. *Science Immunology, 9*(100), eadg6453. doi: 10.1126/sciimmunol.adg6453.
- Engleman, E. G., & Bagchi, S. (2024). *U.S. Patent Application No. 18/683,174*.

Patents

- Published Application: WO2023023587
- Published Application: 20240368271

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