The Use of Fucose to Increase TILs for the Immunotherapy of Melanoma

Fucose is a hexose deoxy sugar that makes up the fundamental sub-unit of the seaweed polysaccharide fucoidan. Treating melanoma with fucose is a method of enhancing immunotherapy by increasing the number of tumor infiltrating lymphocytes (TILs), especially CD4+ T cells that are more effective in recruiting other immune cells, including CD8+ T cells, DCs, and NK cells. In a mouse model, L-fucose supplementation reduced tumor growth by greater than 65% and significantly increased tumor infiltration by immune cells by 10-50 fold per gram of tumor.

COMMERCIAL OPPORTUNITY

- Melanoma is a type of skin cancer that begins in the melanocytes. Melanoma is less common than basal cell and squamous cell skin cancers but more dangerous because it's much more likely to spread to other parts of the body if not caught early. The American Cancer Society estimates that in 2018 there will be 91,270 patients who develop melanoma and 9,320 melanoma patients will die. Melanoma rates have been rising for the last 30 years.
- The standard of care for melanoma treatment is surgery in early stage and immunotherapy in advanced stages, including immune checkpoint inhibitors pembrolizumab (Keytruda), nivolumab (Opdivo), and ipilimumab (Yervoy), as well as high doses of chemotherapy and radiation therapy and then giving patients tumor-infiltrating lymphocytes (TILs). Drugs that target the BRAF protein, such as vemurafenib (Zelboraf) and dabrafenib (Tafinlar), as well as drugs that target the related MEK proteins, such as trametinib (Mekinist) and cobimetinib (Cotellic), have been shown to shrink melanoma. The 5-year overall survival rate for early disease is 95% and 15-20% for advanced disease.
- There is evidence that fucose can be used to enhance immune function. Fucose supplementation is used to treat Leukocyte-adhesion deficiency (LAD), a disease characterized by a rare primary immunodeficiency. LAD is a rare autosomal recessive disorder characterized by defects affecting how white blood cells (leukocytes) respond and travel to the site of a wound or infection resulting in recurrent infections.

TECHNOLOGY

A mouse melanoma model exposed to dietary L-fucose resulted in decreased tumor growth (>65%) and a significant increase in tumor infiltrating lymphocytes, i.e. NK and CD45+ immune cells. Specifically, the concentration of CD4+ and CD8+ was doubled. Mouse melanoma models immunodepleted of either CD4+ or CD8+ cells and treated with fucose revealed loss of CD4+ T cells significantly abrogated tumor suppression and reduced intratumoral CD8+ T cells, DCs, and NK cells. Therefore, CD4+ T cells are required for intratumoral recruitment of these cell types to suppress tumor growth. The presence and cytolytic activity of CD4+ T cells in tumors has been correlated with better patient survival rates and increased responsiveness to immunotherapies.

PUBLICATION/PATENT

- Provisional Patent filed on 10/13/2017 for Drs. Lester, Ruller, Kodumudi, Pilon-Thomas, Lau, and Watson.

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