FOX CHASE CANCER CENTER
TEMPLE HEALTH

Preventing Netrin G1/ NGL1 Engagement as a Novel Mechanism to Improve the Cancer Treatment Efficacy (Ref. No. 484-EC)

Background

Pancreatic cancer is projected to become the second leading cause of cancer related deaths by 2030, due to its abysmal 5-year survival rate. The most common form of pancreatic cancer is pancreatic ductal adenocarcinoma (PDAC), to which treatments are often refractory, and where symptoms only appear in advanced stages of the disease, making few patients eligible for surgical interventions. Specific characteristics of this cancer include desmoplasia, which is a unique fibrous microenvironmental reaction with an expansion of activated cancer associated fibroblasts (CAFs) and the active remodeling of their extracellular matrix. Desmoplastic stroma plays a role in epithelial tumor development and progression whereas homeostatic normal or innate mesenchymal stroma supports a natural tumor suppressive microenvironment. Reprograming desmoplastic stroma back to its restrictive innate state bears the strong therapeutic potential and reinstitution of anti-tumor immune activity. Thus, there remains a need to manipulate desmoplastic stroma, by modulating CAF/matrix functional units, to improve the treatment efficacy.

Summary of the Invention

Researchers at Fox Chase Cancer Center observed that Netrin G1 (a neural pre-synaptic protein) is unexpectedly expressed in the pancreatic stroma and its levels and localization, together with its receptor NGL1, and increased focal adhesion kinase (FAK) activity (phosphor FAK), may serve as a biomarker indicative of active (e.g., tumor promoting) desmoplasia. High levels of Netrin G1 and factors that sustain a constitutive active FAK indicate the presence of a pro-tumor stroma that limits anti-tumor immune activity. Accordingly, the detection of these markers in patient samples (tumor surgical or bodily fluids) may provide information regarding the stroma status (e.g., its condition, and the stage of desmoplasia). Furthermore, preventing engagement of Netrin G1 with its receptor NGL1 can alter the function of the desmoplastic stroma in a way that it can improve the treatment efficacy. Thus, stroma function will be blocked by: i) preventing fibroblasts or materials secreted by fibroblasts from rescuing cancer cells from dying under nutritional stress conditions (like seen in the tumor microenvironment); ii) preventing CAF generated extracellular vesicles from acting to support cancer cell nutrition; iii) preventing fibroblasts or materials secreted from fibroblasts (including extracellular vesicles) from activating immunosuppressive cells and/or inhibiting immunogenic cells, which will promote cancer killing; iv) preventing immunosuppressive cells like macrophages, from maintaining pro-tumorigenic cells like T - cytotoxic and/or NK cells from activation to effectively kill cancer cells; v) preventing fibroblasts and other microenvironmental cells (and possible tumor cell as well) from secreting immunosuppressive factors such as IL-6, IL-8, TGFbeta GM-CSF, CCL20, IL1 beta, and similar and/or glutamine, glutamate, and other pro-tumor amino acids, generating pro-tumoral extracellular matrix, and other factors; vi) preventing communications between neural cells, fibroblastic cells, immune cells, other cells, and/or tumor cells.

Patent Status: A patent application has been filed.

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