Investigating the Role of ITGA6 in Tumor Development

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Integrin Alpha 6 Upregulation and Cleavage Promotes Tumor Metastasis
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Introduction

• Cancer is defined as a disease characterized by abnormal growth of cells due to uncontrollable cell division.
• 14 million people are diagnosed annually and of those 8 million will die, making cancer the most deadly disease.
• Prostate cancer is prevalent in males with over three million people living with this cancer today and a death rate of 1.3%.
• Biomarkers can be used to detect cancers in the body before their growth.

Angiogenesis, Metastasis and Cancer Stem Cells

Angiogenesis: the formation of blood vessels that grow from the tumor into the blood stream. These blood vessels allow cancer cells to migrate to other organs.

Metastasis: the dissemination of cancer cells throughout the body via blood vessels created during angiogenesis, accounting for approximately 90% of all deaths. Cancer Stem Cells: cancer cells are self-renewing cells that co-exist within normal cancer cell populations and give rise to secondary tumors.

Integrin Alpha 6 (ITGA6) in Tumor Development

• Integrins are transmembrane proteins that aid in extracellular and intracellular communication.
• ITGA6 has been found in several cancers including neuroblastomas, prostate, breast, and pancreatic cancer.
• ITGA6 gene expression has been found at both upregulated and downregulated gene expressions leading to increased susceptibility to tumor development.
• ITGA6 also has been shown to be an angiogenic factor, as well as, a factor that affects metastasis.

Manipulation of Human ITGA6 in Zebrafish Cells

Human Full Length ITGA6
The image above shows a model of the Human Full Length ITGA6 construct or genetic manipulation, in which fish cells have an increased amount of ITGA6 on the cell surface.

Human Truncated ITGA6
The image above shows Human Truncated ITGA6 RNA, in which the ITGA6 is truncated or cleaved from the cell, resulting in increased amounts of ITGA6 in the tumor tissue.

Human Mutated ITGA6
The image above shows Human Mutated ITGA6 RNA. In this construct, the ITGA6 is mutated in the cleavable part of ITGA6, resulting in a non-cleavable ITGA6. Zebrafish embryos are injected with their respective RNA at 8hpf.

Labeling of Human PC3 Cancer Cells

Both images display PC3 cells. The image shows labeled PC3 cells with DiI (red) that allow for clear visibility of the cells in the embryo. DiI labeled cells are injected into the embryo at 24hpf.

Using ITGA6 Manipulations in Drug Screening

• Continue Human ITGA6 manipulation at the host level.
• Investigate the effects of manipulating ITGA6 expression in Human PC3 cancer cells, on tumor progression.
• Use the valuable zebrafish tumor xenograft model to conduct a drug screening.

Full Length ITGA6 and α6p May Lead to Metastasis

The graph to the left displays the number of embryos exhibiting metastasis (%) for each ITGA6 construct. A significant p-value of less than 0.01 using a t-test was found in the full length and truncated constructs. This data suggests that both increasing and cleaving ITGA6 lead to increased tumor progression.

The image on the left shows metastasis in the trunk of the body. The image on the right shows no metastases in the zebrafish (control).

Literature Review


Acknowledgements

We acknowledge and thank the Georgia Southern Chemistry Department, Mr. Andy Diamandaris, Dr. Talentino, and the University Honors Program.
To create the Human PC3 Zebrafish Tumor Xenografts, Human ITGA6 RNA is injected into zebrafish embryos (0 hpf). Human PC3 cells are cultured and labeled with DiI cell labeling solution before being injected into the yolk region of zebrafish embryos (24 hpf). Zebrafish embryos are observed daily for metastasis and angiogenesis using the Zeiss AX10 light microscope. Results are then analyzed using immunohistochemistry and laser confocal imaging.