TGFβ Pathway Gene Expression Patterns in Invasive Ductal Breast Carcinoma (IDC) and Glioblastoma Multiforme (GBM)

Briana Soto and Dr. Nancy Liu-Sullivan

Abstract
Glioblastoma multiforme, GBM, is categorized as the most aggressive form of gliomas found along the central nervous system. While gliomas approximately make up 80% of all malignant brain tumors, GBM is responsible for approximately half of all primary brain and CNS cancers. This form of cancer targets more men than women and increases in tumor frequency with age as well. Once diagnosed, patients will typically receive a poor medical prognosis with an average survival rate of 12 to 18 months. Invasive ductal carcinoma, IDC, is one of the most common forms of breast cancer diagnosed in women. Approximately eight out of ten women, who are diagnosed with breast cancer, will be diagnosed with IDC. The tumors will initially form in the milk ducts of breasts but will then infiltrate the surrounding fatty breast tissue. Once GBM and IDC have advanced to stage IV, both cancers will show resistance to standard cancer treatments. The gene expression patterns of both cancers will be studied, through computational analysis and the Oncomine database, in order to determine which set of genes are being over and under expressed. The genes that are over expressed will be used as potential biomarkers and help to shed light on potential molecular targets for novel drug treatments.

Background Information
The fast proliferation of cancer cells in GBM and IDC is due to genetic mutations and unregulated signaling pathways. TGFβ, transforming growth factor β, has tumor suppressive effects, which cancer cells must avoid in order to spread and grow. Since this signaling pathway controls other important cellular functions such as cell invasion, immune regulation and microenvironment modification, the mis-regulation of this pathway results in tumor development. In cancer cells, TGFβ promotes tumor growth, cell invasion, and surpasses immune surveillance. The cancer cells are capable of doing so through two ways. The first way is through the inactivation of the pathway’s receptors and the second way is through downstream alteration that only disable the tumor suppressive capability of the pathway.

Methodology:
- **Oncomine**: A cancer microarray database of genome expression analyses used for the comparison of gene expression in GBM and IDC
- **Excel**: A software system that creates spreadsheets, charts and graphs,
  Each gene was searched on Oncomine in order to compare the expression of genes in the the TGFβ signaling pathway. Three filters were used for each gene searched. The filters used were the differential expression analysis, a comparison of cancer versus respective normal tissue, and with respect to the corresponding cancer. Ten studies were used for each gene and receptor, with the no value as the control and the median of the targeted cancer values for the gene expression pattern. The reverse log 2 values were taken from the original values on Oncomine and were placed on an excel file sheet along with the control data as well. The data was placed in a graphical form in order to see the gene expression pattern.

Results:
The graphical analyses of GBM and IDC, show that IDC has a stronger gene expression patterns with fewer genes being over-expressed. In GBM, the following genes are being over-expressed: TGFβ1, TGFβ3, TGFβRI, TGFβRII, Smad3, Smad4. In IDC, the following genes are being over-expressed: TGFβ3, TGFβRI, and Smad2. Out of the nine genes studied, GBM and IDC both exhibit high gene expression in TGFβ3 and in TGFβRII, and low gene expression with the SARA gene.

TGFβ Signaling Pathway: Cancerous vs. Normal Conditions
- **The TGFβ signaling pathway primary focus is to suppress tumor growth and maintain homeostasis. This is done by regulating cellular differentiation and proliferation, immune surveillance, cell adhesion, apoptosis and suppression of stromal inflammation.**
  Cancerous cells must evade the tumor suppressive effects of TGFβ, in order to enter the malignant stage.
- **TGFβ will signal the promotion of tumor growth, cell invasion, evasion of immune system surveillance, cell dissemination and eventually form metastatic colonies.**
- It is able to modify the cellular environment to benefit the survival and growth of cancerous cells.
- The activation of the TGFβ signaling pathway can lead to resistant cancer types that may not respond to the standard cancer treatments of chemotherapy and radiation.

Discussions and Findings
In GBM, both TGFβRI and TGFβRII are being over-expressed, and IDC only TGFβRI is being over-expressed. This could be due to a potential mutation, in which the receptor itself is becoming active in the absence of TGFβ. If there is no TGFβ present to bind to its corresponding receptor, then the receptor should not be active. The receptors have been able to bypass this mechanism of gene regulation. The over-expression of its receptors, oncogene activation and inactivation of its tumor suppressor effect are some of the root causes for the development of an aggressive and resistant cancer type. It is important to note, that while determining the patterns of gene expression in cancerous cells is a key step in developing potential markers for drug treatments, not every patient will respond the same due to having different genetic expressions. Overall, the highly-expressed gene’s localization and molecular function allows the possibility of developing drug inhibitors and or detection in serums. As a result, therapeutic agents are the most effective against highly expressed genes.

Future Perspectives
The main purpose of this project is to find which genes are being over-expressed. The over-expressed genes would be the correct candidate to use for the development of novel drug therapies. By being able to target and inhibit specific genes and receptors, a better treatment can be developed in order to create a positive prognosis for the patients. The final goal is to be able to use the novel drug in combination with the standard cancer treatments of chemotheraphy and Radiation. One of the future goals is to be able to understand better how the TGFβ signaling pathway affects the genes involved in it and how it affects cancer growth.

References:
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