The Day and Night of Grb2 in Glioblastoma Multiforme

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Abstract:
Growth Factor Receptor Binding Protein – 2 (Grb2) is an essential protein in cell motility, signaling, and most importantly, cell division. In a healthy cell, Grb2 interacts with various growth factors, stimulating the Ras signal transduction pathway, which facilitates cell growth and division. One such growth factor is VEGF (vascular endothelial growth factor), which promotes capillary branching, or angiogenesis. In a cancerous cell, this process goes horribly wrong. Overproduction of VEGF causes overexpression of Grb2 and overstimulation of the Ras pathway, leading to tumor growth. The growing tumor requires greater amounts of oxygen, supplied through angiogenesis, to sustain itself, causing increased production of VEGF and ultimately more tumor growth. Through this process, Grb2’s ability to link angiogenesis and tumor growth can result in deadly cancers, including one of the most severe forms of brain cancer, Glioblastoma Multiforme (GBM). One method of treating this form of cancer targets VEGF, inhibiting both angiogenesis and tumor growth through the Grb2-Ras pathway. One medicine developed for this purpose is Bevacizumab (commonly called Avastin), which has been shown to lower the function of VEGF. By inhibiting the production of VEGF, the overstimulation of Grb2 is negated and, under ideal circumstances, the tumor is deprived of oxygen and nutrients, resulting in atrophy.

Glioblastoma Multiforme

The most common and aggressive grade IV glial tumor (a type of brain cancer)
- 5 of every 100,000 in the USA
- 20% of primary brain tumors
- Most invasive and Grows rapidly
- Most common age 45 or above
- Median survival < 2 years

Most common symptoms:
- Headache, Seizure, Focal neurologic deficits, Change in mental status

Treatment:
- Neurosurgery, radiation therapy and chemotherapy

One of the treatment options is focused on reducing the growth of tumors by inhibiting angiogenesis.
- Avastin (Bevacizumab) therapy

Angiogenesis and Avastin Therapy

Angiogenesis plays a key role in Tumor growth. Angiogenesis is the growth of new blood vessels. In most scenarios, Angiogenesis is considered a healthy process and increases blood circulation. This however is not always the case. In cases of Angiogenesis when one or more tumors are present, the increased blood circulation leads to increased tumor growth and the spread of cancer.

Avastin (Bevacizumab) therapy (anti-angiogenic therapy) for recurrent tumors

Avastin limits the production of Vascular Endothelial Growth Factor (VEGF) by the tumor, thereby inhibiting angiogenesis. This will starve the tumor and lead to its shrinkage.
- Response rate is not same in all individuals.
- 40% are non-responders.

Hence understanding GBM molecular biology is crucial to identify new therapeutic targets.

References

Proteomics of Glioblastoma multiforme

Rat brain inoculated with U87 MG

Inoculate U87 MG human GBM cells

Grows GBM tumors

Treat with or without Avastin

Proteins differentially expressed during tumor growth

Proteins differentially expressed in tumor & as a response to therapy

Results:

Protein expressed as a response to therapy

Growth factor receptor-bound protein 2

Not expressed in tumor suppressor genes 1

Eukaryotic translation initiation factor 5A-1

Beta-soluble NSF attachment protein

Avastin

Grb2 is up-regulated in its expression in sample with no treatment.
Grb2 expression is down-regulated after avastin treatment.

Mass Spectrometry-based Proteomics

Overview

- Mass spectrometry-based proteomics can identify proteins expressed in disease and healthy states.
- Grb2 is up-regulated in its expression in glioblastoma multiforme, and is down-regulated after avastin treatment.
- Protein signatures are unique in glioblastoma multiforme with and without avastin therapy – useful to identify new and alternate potential therapeutic targets.