Glioblastoma pathophysiology:

M.J. van den Bent
The Brain Tumor Center at Erasmus MC Cancer Center
Rotterdam, the Netherlands
Pathophysiology: pathophysiology seeks to explain the physiological processes or mechanisms whereby such condition develops and progresses.

Pathophysiology, glioblastoma & Pubmed: 1174 hits, incl

- Targeting NF-κB in glioblastoma: A therapeutic approach
- JC polyomavirus in the aetiology and pathophysiology of glial tumours
- Role of Nitric Oxide in Glioblastoma Therapy: Another Step to Resolve the Terrible Puzzle?
- The role of ion channels in malignant brain tumors.
- MicroRNA-1908 functions as a glioblastoma oncogene by suppressing PTEN tumor suppressor pathway.
- CRMP5 Controls Glioblastoma Cell Proliferation and Survival through Notch-Dependent Signaling.
- The vacuolar H+ ATPase is a novel therapeutic target for glioblastoma.
- Intersectin1-S, a multidomain adapter protein, is essential for malignant glioma proliferation.
Cancer: bad luck or environment?

- “Variation in cancer risk among tissues can be explained by the number of stem cell divisions”: Most Cancers Caused By Bad Luck?
  - Wu et al: rates of endogenous mutation accumulation by intrinsic processes are not sufficient to account for observed cancer risks²

Hereditary syndromes and glioblastoma

- Li fraumeni: TP53 mutation: breast cancer, sarcoma, glioblastoma
- Turcot syndrome: mutations in mismatch repair genes (MSH6):

The observed stability of brain cancer incidence in Australia between 1982 and 2012 (...) suggests that the observed increases in brain cancer incidence in the older age group are unlikely to be related to mobile phone use
Chapman et al, Cancer Epidemiology, May 5 2016,
http://dx.doi.org/10.1016/j.canep.2016.04.010

Environment factors and glioblastoma

- Ionizing radiation
Chain of events:

Driver vs passenger mutations
Clonal vs subclonal
Changes in the micro-environnement
Essential vs non-essential

Clinical relevance: potential therapeutic targets
The cancer stem cell and subclonal expansion: no linear connection...
TCGA: The Somatic Genomic Landscape of Glioblastoma

The TCGA effort: major improvement of the understanding of the complexity of this disease

- Most glioblastoma are characterized by mutational hits in three major pathways: PI3K pathway, Rb pathway, p53 pathway
- However: at a multitude of different levels, mutually exclusive (e.g., either PTEN mutation/deletion or PI3K mutation)
- “Another level of biological complexity is revealed by targeted proteomic profile, which showed that the impact of specific genomic alterations on downstream pathway signaling is not linear and not always predictably concordant with genotype”

Rb and p53
Altered cell signalling and hallmarks of cancer: EGFR
The hallmark of cancer: six biological capabilities acquired during the multistep development of human tumors.

In addition to cancer cells, tumors exhibit another dimension of complexity: they contain a repertoire of recruited, ostensibly normal cells that contribute to the acquisition of hallmark traits by creating the “tumor microenvironment.”

Hanahan, Weinberg Cell 2012
Signalling Interactions in the Tumour Microenvironment During Malignant Progression

The microenvironment: another glioblastoma target?

Several microenvironmental changes have been used as targets:

- Inhibition of angiogenesis (bevacizumab, cediranib)
- Inhibition of integrines (cilengitide)
- Immunotherapy (rindopepimut, vaccination strategies, PD1 antibodies)
- Inhibition of matrix metalloproteinases
Immunotherapy and tumors: the immune suppressive tumor

**Immune system: Checks and balances**
- T effector cell
- T regulatory cell
- Antigen Presenting Cell
- Dendritic cell

**Stimulate early T-cell activation**
- CTLA4
- CD27/CD70

**Stimulate APC + Vaccination**
- Tumor fragments: proteins
- Co-stimulatory factors: TNF-α, IL1, CD40L/CD40
- IL10

**Remove T-eff inhibition (anti-PD1)**
- PD-L1/PD1
- TGF-β, VEGF
Glioblastoma, a gordian knot?

Jean-Simon Berthèlemy: Alexander cutting the Gordian Knot