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SnapShot: Glioblastoma Multiforme

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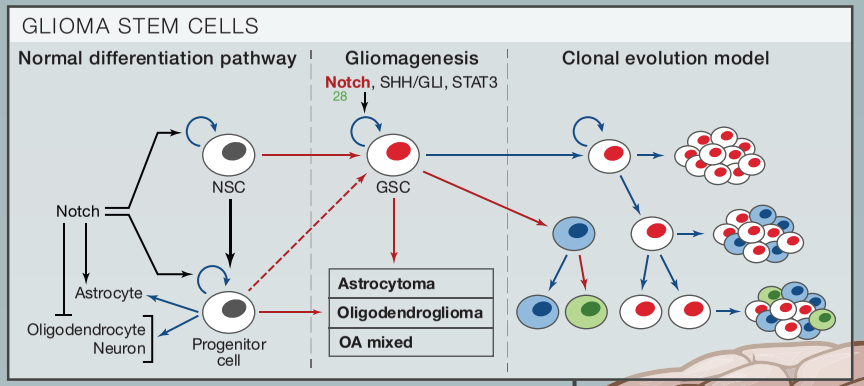

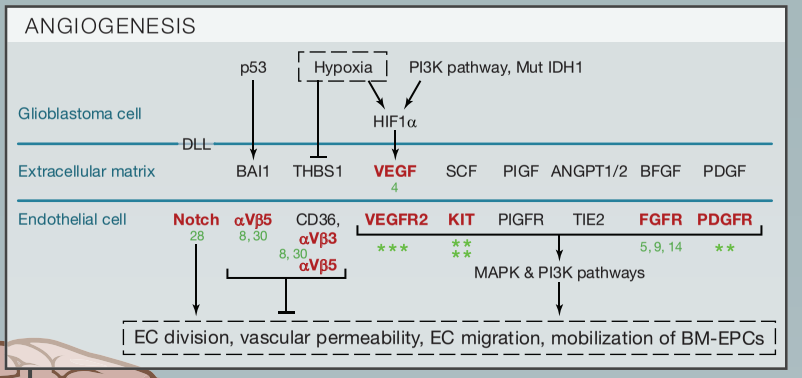

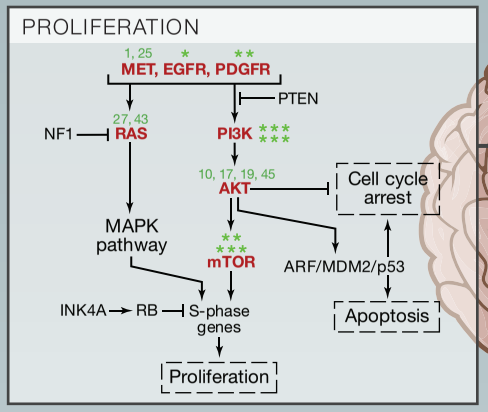

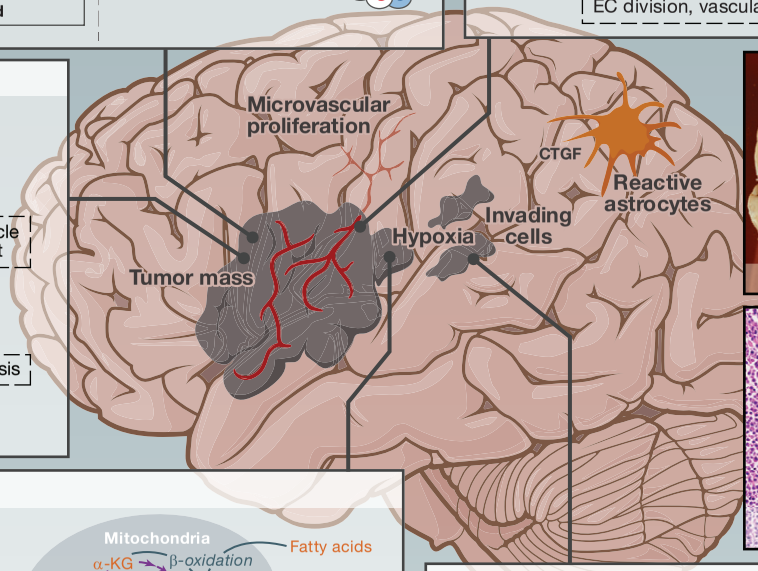

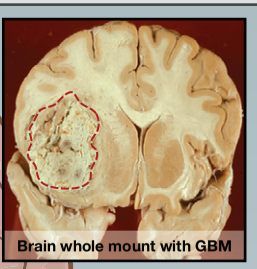

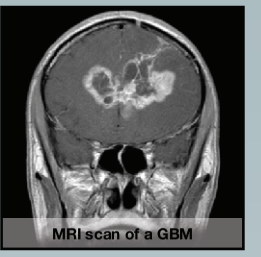

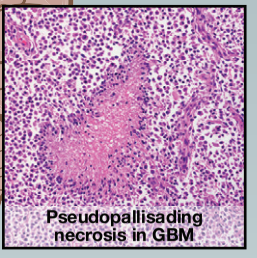

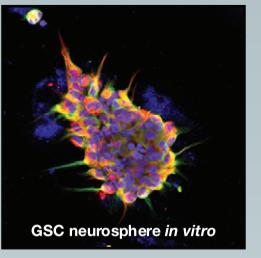

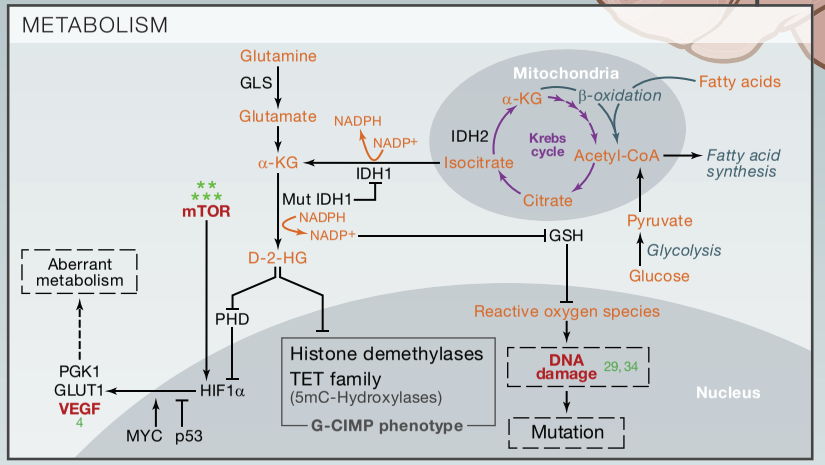

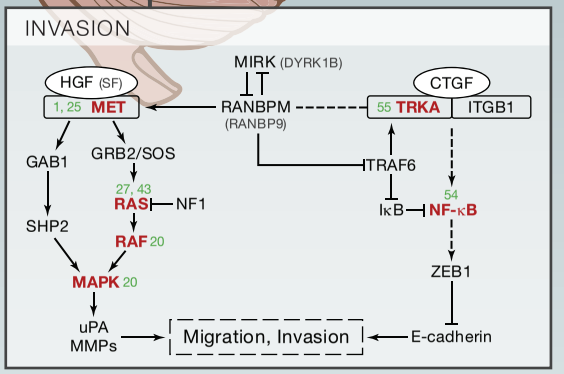

These pharmacological agents affect targets shown in red.	
*	3, 7, 11, 12, 15, 24, 25, 35, 37, 42, 44, 46, 47
**	6, 9, 13, 14, 18, 20, 21, 22, 41, 52
***	2, 5, 6, 9, 14, 18, 20, 21, 24, 25, 36, 39, 40, 52
** **	6, 13, 18, 20, 21, 22, 25
** ***	23, 26, 31, 32, 38, 50, 51
*** ***	10, 16, 26, 33, 48, 53

#	DRUG
1	Rilotumumab
2	Aflibercept
3	Afatimib
4	Bevacizumab
5	Brivanib
6	Cediranib
7	Cetuximab
8	Cilengtide
9	Lenvatinib mesylate
10	Enzastaurin
11	Erlotinib
12	Gefitinib
13	Imatinib
14	Intedanib
15	Lapatinib
16	BKM120
17	Nelfinavir
18	Pazopanib
19	Perifosine
20	Sorafenib
21	Sunitinib
22	Tandutinib
23	Temsirolimus
24	Vandetanib
25	Cabozantinib
26	XL765
27	Tipifarnib
28	R04929097
29	Veliparib
30	ATN-161
31	AZD8055
32	AZD2014
33	BKM120
34	Iniparib
35	Rindopepimut
36	Pegdinetanib
37	Matuzumab
38	Everolimus
39	Foretinib
40	Ramucirumab
41	Olavatumab
42	I-125 MAB-425
43	Lonafarnib
44	ABT-806
45	MK2206
46	Nimotuzumab
47	Dacomitinib
48	PX-866
49	Panobinostat
50	Ridaforolimus
51	Sirolimus
52	Vatalanib
53	XL147
54	Bortezomib
55	AZD7451

See online version for legend and references.

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Glioblastoma multiforme (GBM) is the most common and lethal type of primary brain tumor. Although nonmetastasizing, GBM cells can diffusely infiltrate the normal cerebral cortex, resulting in death, with a median survival of 14 months despite combined surgical resection, radiotherapy, and chemotherapy. Standard therapy has been relatively ineffective for many reasons, not the least of which is the extensive invasion of GBM cells into normal brain tissue, which limits the extent of surgical resection and high dose radiotherapy for fear of unacceptable permanent neurological damage to the patient. Traditional chemotherapy has limited value because of poor blood-brain barrier penetration, intrinsic glioma resistance, and nonselective toxicity. Thus, the development of improved therapies rests on a greater understanding of the biology of GBM.

Several molecular and genomic datasets have recently been generated that have allowed us to identify at least four subtypes of GBM: classical, mesenchymal, proneural, and neural. **Classical** subtype is characterized by chromosome 7 amplification, focal *CDKN2A* deletion, chromosome 10 loss, *EGFR* amplification/mutation, a lack of *TP53* mutations, RB pathway alterations, *NES* expression, and high Notch and Hedgehog pathway activity. **Mesenchymal** subtype has frequent mutation or loss of *NF1*, *TP53*, and *PTEN*; frequent chromosomal aberrations at *CDK6*, *MET*, *PTEN*, *CDKN2A*, and *RB1* loci; activation of NF-κB and TNF pathways; and overexpression of MET, CD44, MERTK, and CHI3L. **Proneural** subtype frequently has *IDH1* or *IDH2* mutations; *PDGFR* amplification or *PIK3CA*/*PIK3R1* mutations; loss or mutation of *TP53*, *CDKN2A*, and *PTEN*; activation of HIF, PI3K, and PDGFR pathways; OLIG2, NKX2-2, and PDGFRA oligodendrocytic marker expression; and TCF4, SOX, DCX, DLL3, and ASCL1 proneural marker expression. **G-CIMP** methylator phenotype characterizes a subgroup of proneural GBM that may represent a distinct tumor type. **Neural** subtype is related to the classical subtype but has a higher frequency of *TP53* mutation; *EGFR* amplification/overexpression; and NEFL, GABRA1, SYT1, and SLC12A5 neuronal marker expression.

The traditional strategy in oncology of attempting tumor eradication has been challenged with the concept that even without killing every last cancer cell, interfering with critical aspects of tumor biology may translate to significant clinical benefit. The accompanying SnapShot diagrammatically captures several key biological properties and the responsible molecular pathways that represent the current focus of GBM clinical trials.

Proliferation

Cell cycle deregulation in GBMs is in part a result of abnormal signaling by several different receptor tyrosine kinases (RTKs) including EGFR, PDGFR, and MET. These RTKs act downstream to deregulate MAPK and PI3K pathways. The greatest emphasis in targeted drug development for GBM has focused on RTK inhibitors. Recent preclinical and clinical work indicates redundancy in RTK signaling, suggesting the need for simultaneous inhibition of multiple RTKs or inhibition of downstream signals; hence, there has been great interest in the clinical testing of inhibitors of PI3K, AKT and the TORC1/2 complexes. Although there was an initial interest in CDK inhibitors, early clinical data suggest nonselectivity of the agents and toxicity to normal proliferating cells.

Metabolism

GBMs, like other tumors, prefer aerobic glycolysis (a phenomenon known as the Warburg effect). Preclinical data has demonstrated a dependency on altered glucose and fatty acid metabolism, but drugs that selectively interfere with these biochemical pathways are only now coming into clinical development. This altered metabolism also results in the generation of excess reactive oxygen species (ROS), which has led to the development of several new agents that interfere with the GBM cell's ability to neutralize ROS. Moreover, about 80% of low grade gliomas and about 5%–10% of GBMs have mutations in *IDH1* or *IDH2* causing altered 2-hydroxyglutarate production and altered DNA methylation, which has led to trials with IDH1 inhibitors and demethylating agents to address the epigenomic changes associates with this genotype.

Glioma Stem Cells

There is increasing evidence that only a subpopulation of cells within a GBM truly has tumorigenic properties. The nature of these cells remains controversial, but it is clear that at least some canonical stem cell signaling pathways are operative in glioma stem/initiating cells (GSCs). It appears that Notch signaling is vital for proliferation and survival of GSCs, leading to a series of clinical trials in GBM with γ-secretase inhibitors. There is also evidence to suggest that at least some GSC lines are dependent on the Hedgehog and Wnt pathways, paving the way for clinical trials with Smo inhibitors and inhibitors of Wnt ligands.

Angiogenesis

GBMs are highly angiogenic and vasculogenic. VEGF is a primary mediator of tumor angiogenesis and GBM-associated cerebral edema. Anti-VEGF bevacizumab can significantly decrease cerebral edema and potently inhibit tumor growth in patients. Small molecule inhibitors of VEGFR, however, have proven less effective in the clinic to date. Ongoing clinical trials are investigating agents that target other angiogenic factors and their receptors (e.g., PDGFR, c-KIT, FGFR) as well as endothelial cell-associated integrins.

Invasion

Since GBMs generally kill via their invasiveness, patient morbidity and survival might be greatly improved by inhibiting invasion. PI3K and MAPK pathway deregulation has been linked with increased cellular motility via EGFR signaling in GBM. Amplification and/or overexpression of the HGF/MET pathway have also been implicated in GBM invasion, leading to clinical trials of MET inhibitors. Recently, TRKA has been implicated as an important mediator of GBM stem cell migration, leading to the testing of novel TRK inhibitors.

It is unlikely that inhibiting any one pathway will result in dramatic clinical benefit, but it is hoped that interfering with two or more key biological functions will. For example, recent preclinical and clinical data suggest that VEGF inhibition leads to increased GBM invasiveness. New clinical trials, therefore, are now being developed to combine angiogenic inhibitors such as bevacizumab with MET and/or TRK inhibitors. These future trials likely hold the most promise for improved therapy for this devastating disease.

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