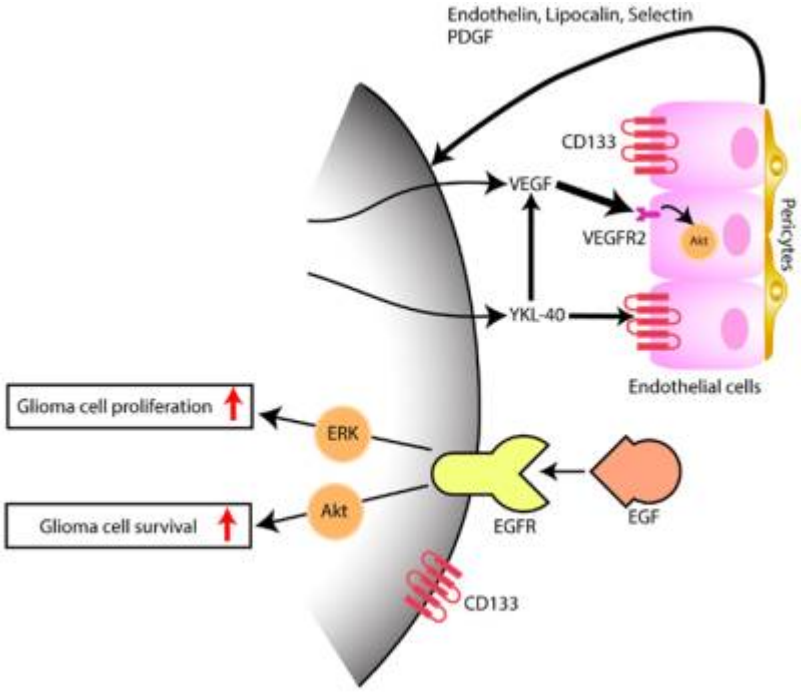
YKL40



Chitinase-3-like protein 1 (CHI3L1), also known as YKL-40, is a secreted glycoprotein that is approximately 40kDa in size that in humans is encoded by the CHI3L1 gene.

The name YKL-40 is derived from the three N-terminal aminoacids present on the secreted form and its molecular mass. YKL-40 is secreted by various cell-types including macrophages, chondrocytes, and some types of cancer cells. YKL-40 lacks chitinase activity due to mutations within the active site (conserved sequence: DXXDXDXE ; YKL-40 sequence: DGLDLAWL). The exact physiological role of YKL-40 is not known, but it has been implicated in development, inflammatory disease (such as asthma, and cancer progression).

There is evidence for over-expression of the YKL40 gene in high grade gliomas. The high serum levels of the glycoprotein are associated with poor prognosis of various inflammatory and tumour processes.

YKL40 may be a novel key molecule in addition to MGMT, that is responsible for TMZ resistance in glioblastoma cell lines and could be a new target to overcome TMZ resistance in recurrent glioblastomas in the future [1)].

In a study, Cardona et al., explored the efficacy of carmustine plus bevacizumab (BCNU/Bev) for treating rGBM.

They assessed 59 adult patients with histologically confirmed rGBM who were treated with BCNU/Bev as second-line regimen. The response rate (RR), progression free survival (PFS) and overall survival (OS) were evaluated according to their molecular expression profile, including CD133 mRNA expression, MGMT methylation (pMGMT), PDGFR amplification, YKL40 mRNA expression, IDH1/2 condition, p53 and EGFRvIII mutation status.

Median follow-up was 18.6 months, overall RR to the combination was 56.3%, and median PFS was

9.0 months (95% CI 8.0-9.9). OS from time of diagnosis was 21.0 months (95% CI 13.2-28.7) and from starting BCNU/Bev it was 10.7 months (95% CI 9.5-11.8). IDH1/2 mutations were found in 30.5% of the patients, pMGMT in 55.9% and high CD133 mRNA expression in 57.6%. Factors which positively affected PFS included performance status ($p = 0.015$), IDH+ ($p = 0.05$), CD133 mRNA expression ($p = 0.009$) and pMGMT+ ($p = 0.007$). OS was positively affected by pMGMT+ ($p = 0.05$). Meanwhile, YKL40 negatively affected PFS ($p = 0.01$) and OS ($p = 0.0001$). Grade ≥ 3 toxicities included hypertension (22%) and fatigue (12%).

BCNU/Bev is a safe and tolerable treatment for rGBM. Patients with MGMT+/IDH+ derive the greatest benefit from the treatment combination in the second-line setting. Nonetheless, high YKL40 expression discourages the use of antiangiogenic therapy [2].

Kazakova et al., investigated the YKL40 mRNA level and protein expression in the tumour site and in the serum of high-grade glioma patients. The YKL-40 expression in 36 patients with glial tumours (astrocytoma grade III, glioblastoma) and 33 age-matched healthy persons was measured by gene analysis, immunohistochemistry and ELISA. YKL-40 serum levels in high-grade glioma patients compared to healthy subjects were significantly increased ($P \leq 0.05$). A wide range of variability in YKL40 mRNA expression was found. YKL-40 staining in situ was more abundant in glioblastoma tissue than in anaplastic astrocytoma, with the lowest level in normal brain tissue. Our gene analysis revealed that in general, YKL40 mRNA in glioma patients was over-expressed versus normal brain. A significant correlation between YKL40 transcript and protein levels was observed ($P \leq 0.05$). It could be speculated that the YKL-40 protein might contribute to glioblastomas' specific biological characteristics that distinguish them from grade III gliomas. A complex investigation of YKL40 expression was performed at the molecular and cellular levels in human high-grade gliomas. Serum YKL-40 concentrations increased with tumour grade and correlated positively with transcript rate, being the highest in glioblastoma. We provide evidence for a relationship between YKL40 expression and the malignancy of glial tumours [3].

References

1)
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