Heat shock protein 90

Heat shock protein 90 (HSP90) is a regulator of the stability of oncogenic proteins including EGFR, thereby acting as a molecular chaperone.

Zhu et al. reported a medium-throughput drug screening platform (METPlatform) based on organotypic cultures that allow evaluating inhibitors against metastases growing in situ. By applying this approach to the unmet clinical need of brain metastases, they identified several vulnerabilities. Among them, a blood-brain barrier permeable HSP90 inhibitor showed high potency against mouse and human brain metastases at clinically relevant stages of the disease, including a novel model of local relapse after neurosurgery. Furthermore, in situ proteomic analysis applied to metastases treated with the chaperone inhibitor uncovered a novel molecular program in brain metastases, which includes biomarkers of poor prognosis and actionable mechanisms of resistance. The work validates METPlatform as a potent resource for metastases research integrating drug screening and unbiased omics approaches that are compatible with human samples. Thus, this clinically relevant strategy is aimed to personalize the management of metastatic disease in the brain and elsewhere [1)].

We investigated the expression of EGFR and its chaperone HSP90 in Glioblastoma, IDH-wildtype. Tissue availability permitted analysis of 237/449 consecutive Glioblastoma cases, among them 214 IDH-wildtype (90.3%). The expression of EGFR and HSP90 was analysed by immunohistochemistry on a tissue microarray containing various tumour regions. The expression intensity (EI), and an expression score (ES) combining the percentage of stained cells with EI were determined for both markers. Overall, there was a positive correlation between EGFR and HSP90 expression (EI; r=0.275, P<0.001; ES, r=0.333, P<0.001). The expression of EGFR and HSP90 was significantly higher in the tumour centre, compared to the infiltration front (EI, P=0.002; ES, P<0.001). Survival data were available in 96 IDH-wildtype cases, and high expression of EGFR (ES only) was in trend associated with better outcome, but failed to meet statyistical significance (P=0.061). A combination of EGFR and HSP90, however, discriminated between different prognostic groups, with EGFRlow/HSP90low tumours showing the worst prognosis in univariate analysis (P=0.001), and in multivariate analysis including the other relevant prognostic factors age, MGMT status and postoperative treatment [n=76; hazard ratio (HR)=0.571; 95% confidence interval (CI) 0.328-0.996; P=0.048]. EGFR expression stratified most pronounced among HSP90low tumours, where the EGFRhigh phenotype was associated with longer survival. Our results reveal a variable reliance on the signalling pathway by EGFR in Glioblastoma, IDH-wildtype. Low co-expression was associated with worse prognosis [2)].

1)

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2)
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