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Effects of EGFR-MEK-ERK pathway on PD-L1 expression in head and neck squamous cell carcinoma

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Objectives: Programmed death ligand-1 (PD-L1) is frequently expressed in human cancers, including head and neck squamous cell carcinoma (HNSCC). However, the regulation of PD-L1 in HNSCC remains largely elusive. The purpose of this study was to address the molecular mechanism of PD-L1 regulation by EGFR-MEK-ERK signaling and to suggest potential clinical relevance of blocking PD-1/PD-L1 in combination with therapeutic options targeting EGFR signaling in HNSCC.

Methods: Correlations of PD-L1 protein expression and key nodes of EGFR-MEK-ERK signaling in HNSCC were analyzed by The Cancer Proteome Atlas (TCPA, http://tcpaportal.org). The impact of drugs targeting the EGFR-MEK-ERK pathway on tumor cell survival, clonal expansion as well as PD-L1 expression were addressed in cell culture models. PD-L1 expression and ERK1/2 phosphorylation (p-ERK1/2) were assessed on tissue microarrays with specimens from primary oropharyngeal squamous cell carcinoma (OPSCC) (n=123 patients) by immunohistochemistry and were compared with clinic-pathological features.

Results: A highly significant association was found between PD-L1 expression and key nodes of EGFR-MEK-ERK signaling analyzing the TCPA-HNSCC dataset. However, no significant association was found between PD-L1 expression and p-ERK1/2 protein level in the TCPA-HNSCC dataset OPSCC cohort. The impact of cetuximab on PD-L1 expression in HNSCC cell lines after short-term or long-term treatment was heterogeneous but independent of ERK1/2 phosphorylation. Treatment with a MEK1/2 inhibitor confirmed that PD-L1 regulation in HNSCC cell lines is largely independent of MEK-ERK signaling. The majority of HNSCC cell lines with long-term cetuximab treatment regained ERK1/2 phosphorylation as compared to short-term treatment. Up-regulation of PD-L1 was observed in most cetuximab-resistant cell lines after long-term treatment.

Conclusion: Our findings suggest a complex and context-dependent PD-L1 regulation upon inhibition of the EGFR-MEK-MAPK signaling cascade and further experimental and clinical studies will be essential to unravel underlying molecular principles.