Dokumenttyp: journal article

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Abstract: PURPOSE: To identify pretherapeutic predictive biomarkers in tumor biopsies of patients with locally advanced esophageal adenocarcinomas treated with neoadjuvant chemotherapy, we used an explorative proteomic approach to correlate pretherapeutic protein expression profiles with tumor response to neoadjuvant chemotherapy. EXPERIMENTAL DESIGN: Thirty-four patients with locally advanced esophageal adenocarcinomas who received neoadjuvant platin/5-fluorouracil-based chemotherapy before surgical resection were enrolled in this study. Response to chemotherapy was determined (a) by the amount of decline of [18F]fluorodeoxyglucose tumor uptake 2 weeks after the start of chemotherapy measured by positron emission tomography and (b) by histopathologic evaluation of tumor regression after surgical resection. Explorative quantitative and qualitative protein expression analysis was done through a quantitative differential protein expression analysis that used dual-isotope radioactive labeling of protein extracts. Selected identified biomarkers were validated by immunohistochemistry and quantitative real time reverse transcription-PCR. RESULTS: Proteomic analysis revealed four
cellular stress response-associated proteins [heat-shock protein (HSP) 27, HSP60, glucose-regulated protein (GRP) 94, GRP78] and a number of cytoskeletal proteins whose pretherapeutic abundance was significantly different (P < 0.001) between responders and nonresponders. Immunohistochemistry and gene expression analysis confirmed these data, showing a significant association between low HSP27 expression and nonresponse to neoadjuvant chemotherapy (P = 0.049 and P = 0.032, respectively). CONCLUSIONS: Albeit preliminary, our encouraging data suggest that protein expression profiling may distinguish cancers with a different response to chemotherapy. Our results suggest that response to chemotherapy may be related to a different activation of stress response and inflammatory biology in general. Moreover, the potential of HSPs and GRPs as biomarkers of chemotherapy response warrants further validation.

Zeitschriftentitel / Abkürzung:
Clin Cancer Res

Jahr:
2008

Band:
14

Heft / Issue:
24

Seiten:
8279-87

Sprache:
eng

Pubmed:

Print-ISSN:
1078-0432

TUM Einrichtung:
Institut für Allgemeine Pathologie und pathologische Anatomie ; III. Medizinische Klinik und Poliklinik ; Nuklearmedizinische Klinik und Poliklinik

Occurences:
- Einrichtungen > Fakultäten > Fakultät für Medizin > Kliniken und Institute > Institut für Allgemeine Pathologie und Pathologische Anatomie > 2008
- Einrichtungen > Fakultäten > Fakultät für Medizin > Kliniken und Institute > Klinik und Poliklinik für Nuklearmedizin > 2008
- Einrichtungen > Fakultäten > Fakultät für Medizin > Kliniken und Institute > III. Medizinische Klinik und Poliklinik (Hämatologie / Onkologie) > 2008

entries: