Integrin alphavbeta3 mediates upregulation of epidermal growth-factor receptor expression and activity in human ovarian cancer cells.

Abstract:

Upon overexpression of integrin alphavbeta3 and its engagement by vitronectin, we previously showed enhanced adhesion, proliferation, and motility of human ovarian cancer cells. By studying differential expression of genes possibly related to these tumor biological events, we identified the epidermal growth-factor receptor (EGF-R) to be under control of alphavbeta3 expression levels. Thus in the present study we characterized alphavbeta3-dependent changes of EGF-R and found significant upregulation of its expression and activity which was reflected by prominent changes of EGF-R promoter activity. Upon disruption of DNA-binding motifs for the transcription factors p53, ETF, the repressor ETR, p50, and c-rel, respectively, we sought to identify DNA elements contributing to alphavbeta3-mediated EGF-R promoter induction. Both, the p53- and ETF-mutant, while exhibiting considerably lower EGF-R promoter activity than the wild type promoter, retained inducibility by alphavbeta3. Mutation of the repressor motif ETR, as expected, enhanced EGF-R promoter activity with a further moderate increase upon alphavbeta3 elevation. The p50-mutant displayed EGF-R promoter activity almost comparable to that of the wild type promoter with no impairment of induction by alphavbeta3. However, the activity of an EGF-R promoter mutant displaying a disrupted
c-rel-binding motif did not only prominently decline, but, moreover, was not longer responsive to enhanced alphavbeta3, involving this DNA element in alphavbeta3-dependent EGF-R upregulation. Moreover, alphavbeta3 did not only increase the EGF-R but, moreover, also led to obvious co-clustering on the cancer cell surface. By studying alphavbeta3/EGF-R-effects on the focal adhesion kinase (FAK) and the mitogen activated protein kinases (MAPK) p44/42 (erk(-1)/erk(-2)), having important functions in synergistic crosstalk between integrins and growth-factor receptors, we found for both significant enhancement of expression and activity upon alphavbeta3/VN interaction and cell stimulation byEGF. Upregulation of the EGF-R by integrin alphavbeta3, both receptor molecules with a well-defined role as targets for cancer treatment, might represent an additional mechanism to adapt synergistic receptor signaling and crosstalk in response to an altered tumor cell microenvironment during ovarian cancer progression.