Could the truncated variant of ERBB2 be present in the squamous carcinomas of the cervix?

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Abstract ERBB2, a ligand-less membrane receptor, is frequently overexpressed in a number of human tumors, contributing to uncontrolled cell proliferation. In some cases, gene amplification correlates with protein overexpression and predicts response to trastuzumab. We analyzed the expression of ERBB2 in a group of 40 patients diagnosed with infiltrating squamous cervical carcinomas (ISCC) using a microarray. Immunohistochemistry was performed using two different antibodies, one against the extramembrane domain and the other one for the intramembrane domain. Ten of the 40 cases included in the study could not be evaluated. Of the 30 remaining biopsies, 13 (42%) showed immunoreactivity only with the antibody against the intramembrane domain. In 5 (16.12%), both intramembrane and extramembrane immunoreactivity was observed, and 12 (40%) were negative for both antibodies. Looking at our results, we propose that, in some ISCC, there is a rupture of the ERBB2 receptor, and this event, with slight genetic amplification, could explain the unfavorable response to trastuzumab observed in some ISCC described for some authors.

Keywords Cervical lesions · IHC · ERBB2

ERBB2, a ligand-less membrane receptor, is frequently overexpressed in a number of human tumors, contributing to uncontrolled cell proliferation. It is encoded by the ERBB2 genes, located at 17q11–2q12. The ERBB2 status is routinely determined in breast cancer patients, either by immunohistochemistry—with antibodies against the extramembrane domain of the protein—or fluorescence in situ hybridization. Gene amplification, present in 25% of the patients, correlates with protein overexpression and predicts a good response to the therapeutic monoclonal antibody trastuzumab (Herceptin®), which binds to p185ERBB-2 at the cell surface [1].

Although the number of infiltrating squamous cervical carcinomas (ISCC) with ERBB2 amplification is low, three or four copies of the gene have been reported in some patients [2–3]. With respect to protein expression, the percentage of tumors with immunoreactivity increases with the grade of the dysplasia with the highest values in the ISCC group [4].

We analyzed the expression of ERBB2 in a group of 40 patients diagnosed with ISCC using a microarray that included two cylinders of 1 mm per case. Immunohistochemistry was performed using a semiautomated system (TechMate 500 Dako Corporation, Golstroup Denmark) after antigen
retrieval at 110°C for 1 min in an autoclave. The method involved the incubation with an anti-ERBB2 antibody using the dextran peroxidase technique (Dako Envision, Glostrup, Denmark) and an automated system (Ventana, Tucson, AZ, USA). Antibodies against the extramembrane (anti-ERBB2 Dako, Glostrup, Denmark) and the intramembrane domain of ERBB2 (anti-ERBB2 CB11 Zymed Lab, San Francisco, CA, USA) were used. Two independent observers scored each biopsy. Ten of the 40 cases included in the study could not be evaluated. Of the 30 remaining biopsies, 13 (42%) showed immunoreactivity only when using the antibody against the intramembrane domain. In 5 (16.12%), both intramembrane and extramembrane immunoreactivity was observed, and 12 (40%) were negative for both antibodies.

The ERBB2 receptor undergoes a proteolytic shedding of its ectodomain that can be detected in the serum of advanced breast cancer patients. In addition, this process leaves in the cell membrane an NH2-terminally truncated fragment, p95ERBB2, which has in vitro kinase activity and is probably constitutively active. This fragment cannot be detected using antibodies against the ERBB2 extramembrane domain, and trastuzumab cannot bind to it. In breast tumors, the presence of p95ERBB2 correlates with a worse prognosis [1] and a poor response to treatment with Herceptin® [5].

Rosty et al. [3] postulated an unfavorable response for cases of SCC to treatment with anti-ERBB2 due to the slight genic amplification. Looking at the results obtained in this study and keeping in mind the writings of other authors, we could propose that the rupture of the receptor, as well as the slight genetic amplification, could explain the unfavorable response to trastuzumab observed in ISCC.

**Conflict of interest statement** We declare that we have no conflict of interest.

**References**