学位論文の要約

様式1-4

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主論文の題名

Heterogeneity of neuroblastoma cell lines in IGF-1 receptor/Akt pathway-mediated cell proliferative responses

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主論文の要約

Introduction（導入）

Insulin-like growth factor 1 receptor (IGF-1R) is critical for cancer cell proliferation; however, recent clinical anti-IGF-1R trials did not s how clear clinical benefit in cancer therapy.

Background（背景）

Neuroblastoma (NB), a malignant tumor that originates from the sympathetic nervous system, is one of the most frequent pediatric solid tumors. Insulin and insulin-like growth factors (IGFs, including IGF-1 and 2) belong to a family of mitogenic growth factors. The IGF-1R inhibitors including IGF-1R neutralizing antibodies, IGF-1 mimetics, and IGF-1R anti-sense/siRNA have been shown to block cancer cell proliferation. Although IGF-1R and the stimulatory ligands (IGFs and insulin) are important for cancer proliferation, anti-IGF-1R therapy has not shown enough clinical benefits in randomized phase III trials.

Objectives（目的）

To clarify the heterogeneous mediation of IGF-1R signaling in NB cell lines.

Methods（方法）

We hypothesized that IGF-1R signaling-mediated proliferative response is heterogeneous in neuroblastoma (NB) cells, and analyzed the cell growth of 31 NB cell lines cultured in 3 different media, including Hybridoma-SFM medium (with insulin) and RPMI1640 with/without 10% FBS. Three growth patterns were found. In response to IGFs and insulin, cell proliferation and Akt phosphorylation were up-regulated in 13 cell lines, and suppressed by MK2206 (Akt inhibitor) and picropodophyllin (PPP, IGF-1R inhibitor).

Results（結果）

3 of these 13 cell lines showed Akt self-phosphorylation and cell proliferation in RPMI1640; their proliferation was down-regulated by anti-IGF-1 or anti-IGF-2 neutralizing antibody, suggesting the existence of autocrine loop in the IGF-1R/Akt pathway. Eighteen NB cell lines did not proliferate in RPMI1640, even though Akt phosphorylation was up-regulated by IGFs and insulin.

Consideration（考察）

Based on the heterogeneous response of the IGF-1R/Akt pathway, the 31 NB cell lines could be classified into group 1 (autocrine IGFs-mediated), group 2 (exogenous IGFs-mediated) and group 3 (partially exogenous IGFs-mediated) NB cell lines.

Conclusion（結論）

These results indicate that the response of the IGF-1R/Akt pathway is an important determinant of the sensitivity to IGF-1R antagonists in NBs. To our knowledge, this is the first report describing heterogeneity in the IGF-1R/Akt-mediated proliferation of NB cells.