Institutionen för Kvinnors och Barns Hälsa

Pluripotent Stem Cell-Derived Teratoma Presents An Embryonic Neoplastic Niche For In Vivo studies Of Neuroectodermal Childhood Tumors

AKADEMISK AVHANDLING
som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i Cancer Centrum Karolinska förläningssal, R8:00, Karolinska Universitetssjukhuset, Solna

Fredagen den 2 november, 2012, kl 09.30

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Stockholm 2012
Abstract

Therapy-resistance and relapse remain problematic in many cancer patients, despite the advancement in anti-cancer therapies. There is a constant need of developing new anti-cancer drugs to combat tumors keeping in mind also the increasing incidence rate of cancers as well as the incidences of relapse. Successful development of new drugs strongly depends on the predictability of the employed preclinical model. Currently used animal models (mostly xenografts and to some extent also gene modified animals) have resulted in progress but still experience some limitations. Many anti-cancer drugs have shown to be working in preclinical models, but proved ineffective in patients. It is therefore very important to develop better pre-clinical models providing and improving clinically relevant predictions should be developed.

This study was carried out to test a novel pre-clinical model originally suggested by Tzukerman et al 2003, using pluripotent stem cell induced teratoma (PSCT). For characterization of this experimental microenvironment, early and late events were studied in PSCT generated from the embryonic stem cell line HS181. Paper I demonstrated the occurrence of a benign embryonic process including increasingly chaotic embryonic tissues. An emerging organoid development was observed exhibiting cellular differentiation with close resemblance to that of the developing human embryo. Presence of also neural areas with prolonged immaturity was frequently observed, and with a morphology similar to that appearing in malignant tumors.

We hypothesized from this that areas of immature neural condensation in PSCT may provide a growth supporting neoplastic niche for neuroectodermal tumors. The findings in paper II and III suggested that the microenvironment in PSCT provide adequate support for growth of neuroectodermal tumors, preferably of childhood origin. To test for clinical relevance of these findings, we next evaluated the PSCT for in situ growth and progression of fresh or frozen/thawed tumor biopsy materials obtained from the surgery of childhood tumor patients at the Karolinska University Hospital.

Sections from the PSCT model demonstrated unique in vivo capturing of progression and micro invasion of the transplanted patient primary tumors - with striking similarities to the tumor conditions in the young patient. Further, an engraftment tropism was observed for implanted tumor cell lines, as well as for patient tumor specimens. In particular, a Neuroblastoma and a Supratentorial primitive neuroectodermal tumor revealed a clear tropism for engraftment in that the Neuroblastoma exclusively incorporated into looses mesenchyme and the Supratentorial primitive neuroectodermal tumor into condensing neural ectoderm.

In conclusion, we have demonstrated that PSCT delivers an in vivo environment allowing childhood neuroectodermal tumors to maintain most of their original characteristics from the patient. This suggest that the PSCT environment is especially well suited for the assessment, and a strong complementary pre-clinical model for in vivo studies of these tumors.

ISBN 978-91-7457-898-0