J. Biol. Res. 2006 n. 1 - Vol. LXXXI - Rubbettino - Soveria Mannelli

CDX2 Expression in ovarian teratomatous cells with intestinal differentiation

M. Mora, L. Mastracci, F. Grillo, G. Gaggero, E.Fulcheri

Departments of Pathology (DI.C.M.I.), University of Genoa

KEY WORDS: cdx2, mature teratomas, intestinal differentiation.

Abstract

Teratomas constitute one of the more common ovarian tumor in childhood. They have often a cistic gross appeareance, but they can also be soiid. They have origin from the germ cell, that is able to develop according to all three germ layers, with different maturation grades: so they are classified as immature (malignant teratoma), if composed of a mixture of adult and embryonal tissues, and mature (benign teratoma), if composed only of mature adult tissues. According to the best theories, these tumours have probably parthenogenetic origin from a single germ cell after the first meiotic division. In a classic microscopy study, some authors found ectodermal derivatives in 100% of the tumours, mesodermal structures in 93%, and endodermal derivatives in 71%. Skin and neural tissue are common, such as bone, cartilage and respiratory tissue; intestinal epithelium is unusual.

In teratoma, a constituent tissue can develop into a malignant tumour in 1% of the cases. Cdx2 gene belongs to the homeobox caudal gene family and it is located, in humans, on the 13q12.3 chromosome; in particular it codifies for a specific nuclear transcription factor which induces intestinal epithelium development, differentiation and preservation. Cdx2 expression in the human embryo can be observed in the intestinal epithelium starting from the sixth week of gestation. In the foetus and in adults it is observed in the whole enteric tube from the duodenum to the anal canal. Our aim is to investigate the expression pattern of cdx2 in teratomatous cells in order to confirm the genic way that germs cells follows in intestinal differentiation.

Introduction

Mature cystic teratomas are germ cell tumours that account for up to 44% of all ovarian neoplasms. They are composed of a variety of tissues usually representing two or three embryonic layers (ectoderm, mesoderm, endoderm) (Scully et al., 1996).

Moreover, they are the most common ovarian tumours in childhood (Ein et al., 1970).

Teratomas have origin from a benign germ, cell which is able to develop according to all three germ layers with different maturation grades: hence, they are classified as immature (malignant teratoma), if composed of a mixture of adult and embryonal tissues, and mature (benign teratoma), if composed of mature adult tissues (Scully et al., 1996).

Many studies have demonstrated that mature teratomas display nuclear sex chromatin (Barr bodies), a 46, XX karyotype and, according to the best theories, they have probably parthenogenic origin from a single germ cell after the first meiotic division (Surti et al., 1990).

Macroscopically, benign teratomas have often a gross cystic appearance, with a white to grey external surface and filled by yellow or brown sebaceous material, but they can also be solid. Microscopically, in a classic study, ectodermal derivatives were found in 100% of the tumours, mesodermal structures in 93%, and endodermal derivatives in 71% (Blackwell et al., 2004).Prevailing ectodermal derivatives are skin and neural tissue; mesodermal derivatives such as bone, cartilage, and fat tissue are usually present; common endodermal tissues include respiratory and intestinal epithelium (Scully et al., 1996).

The differential diagnosis between respiratory epithelium - which often accounts for hyperplasia of mucin-secreting goblet cells - and true intestinal epithelium can be difficult if performed by standard haematoxylin-eosin samples alone. Recently, markers of intestinal differentiation, such as cdx2, have been studied in human neoplastic and non-neoplastic tissues, in order to reveal intestinal components in the samples, finding that in many cases this test could be useful from a diagnostic and therapeutic point of view.

Cdx2 gene belongs to the homeobox caudal gene family. In 1997 it was located, in humans, on the 13q12.3 chromosome

(Drummond et al., 1997). In particular it codifies for a specific nuclear transcription factor, which induces intestinal epithelium development, differentiation, and preservation. Cdx2 expression in the human embryo can be observed in the intestinal epithelium starting from the sixth week of gestation. In the foetus and in adults, it is observed in the whole enteric tube, from the duodenum to the anal canal (Qualtrough et al., 2002).
Our aim is to investigate cdx2 expression pattern in mature teratomas of the ovary, in order to demonstrate a normal development and differentiation of intestinal epithelium in teratomatous context. Moreover, this study could be used to detect intestinal differentiation of teratomatous cells, to perform differential diagnosis with respiratory epithelium, and to accurately evaluate the frequency of intestinal components in mature teratomas.

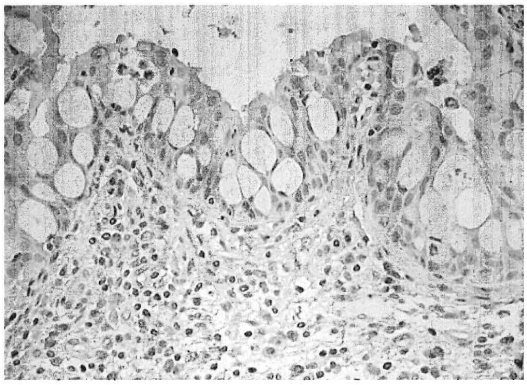

Fig. 1 - Ovarian teratona with respiratory mucosa, cdx2-negative. Cdx2, original magnification 40x.

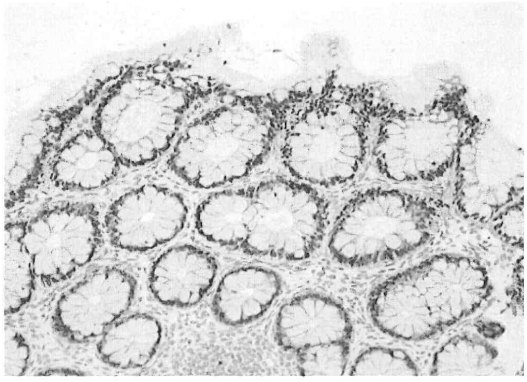

Fig- 2 - Ovarian teratona with intestinal differentiation, cdx-positive. Cdx2, original magnification 20x.

Materials and Methods

A case of ovarian mature teratoma, displaying ectodermal, mesodermal and endodermal derivatives, was obtained from the files of the Departments of Pathology (Di.C.M.I.) of the University of Genoa, and immuno-assayed for cdx2.

Standard staining techniques (H&E) and immunohistochemistry with monoclonal antibodies against cdx2 (Biogenex cdx2-88, batch MU3920402XS) were performed on formalin fixed and paraffin embedded material. Antigen retrieval was performed by microwave, cooking the slides in citrate buffer (pH 6) according to a scheme divided in two steps (the first one lasting 3 min at 900 W and the second one 13 min at 360 W); streptavidin-ABC complex technique with diamino-benzidine as chromogen was used to detect the primary antibody. All immunohistochemical stainings were performed by an automatic stainer (Biogenex OptiMax Plus 2.0) running simultaneously positive and negative controls.

Results

Using anti-cdx2 antibodies the teratomas expressed strong nuclear positivity in foci which showed a clear intestinal differentiation at morphology.

Discussion

On the basis of our results, we suggest that cdx2 expression in mature ovarian teratomas allows to identify foci of intestinal differentiation, even when this observation is made more difficult by the presence of respiratory mucosa, which, on the basis of the previously described confounding morphological aspects, could be misdiagnosed for a true intestinal one. Cdx2-positivity determination in teratomatous cells with intestinal phenotype, moreover, confirms cdx2 activation to be a necessary step in intestinal maturation of a cell.

References

Blackwell WJ, Dockerty MB, Masson JC, Mussey RD. 2004. Dermoid cyst of the ovary. Their clinical and pathological significance. Am J Obstet Gynecol 1946;51: 151-172. In Rosai and Ackerman's Surgical Pathology. Mosby, Edinburgh, ninth edition: pag 1687.

Drummond F, Putt W, Fox M, Edwards YH. 1997. Cloning and chromosome assignment of the human CDX2 gene. Ann Hum Genet Sep;61 (Pt 5): 393-400.

Ein SH, Darte JMM, Stephens CA. 1970. Cystic and solid ovarian tumours in children. A 44-year review. J Pediatric Surg, 5: 148-156.

Qualtrough D, Hinoi T, Fearon E, Paraskeva C. 2002. Expression of CDX2 in normal and neoplastic human colon tissue and during differentiation of an in vitro model system. Gut Aug;51(2): 184-90.

Scully RE, Young RH, Clement PB. 1996. Tumours of the Ovary, Maldeveloped gonads, fallopian Tube, and broad ligament. Washington, DC: Armed Forces Institute of Pathology. Atlas of Tumor Pathology; Third series, Fascicle 23, Cap 14.

Surti U, Hoffner L, Chakravarti A, Ferrell RE. 1990. Genetics and Biology of Human Ovarian Teatimes. I. Cytogenetic Analysis and Mechanism of Origin. Am J Hum Genet. 47:635-643.
–Linder D, McCaw BK, Hecht F. 1985. Parthenogenic origin of benign ovarian teratomas. N Engl J Med.; 152: 896-900.