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Review

Transdifferentiation in neoplastic development and its pathological implication

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Summary. Transdifferentiation is a process in which a cell committed to a particular specialization changes to another quite distinct type. It occurs during embryological development and some pathological processes, and causes the tumor cells to express a phenotype different from that of their normal progenitors. Neoplastic transdifferentiation involves pathogenesis of cancer subtype, transition between neoplastic epithelia and neuroendocrine cell, transition between neoplastic epithelia and mesenchyme, as well as transition between non-neuroectodermal and neuroectodermal cells. We propose that differentiation disturbance of cancer cells should include not only lower-, un-, or de-differentiation, but also transdifferentiation. Tumor cell transdifferentiation results from genetic instabilities. In some type of neoplastic transition, the initiation may be induced by extracellular matrix and growth factors.

Key words: Neoplastic cells, Transdifferentiation, Histogenesis, Genetic instability

Introduction

Differentiation may be defined as the process by which cell achieves its specialization in function and structure. Differentiation implies that a cell has switched on a particular set of genes. Before the phenotype of cell can be expressed and recognized in the differentiation process, there is a stage in which the developmental fate of the cell is established. This status is called cell commitment (or determination). Now we regard commitment as being encoded as a combination of transcription factors present in the cell.

Once cells are committed, their differentiation directions to special phenotypes are stable and inheritable. When a cell's commitment to a particular specialization changes to another quite distinct type, the cell is said to be transcommitted (transdetermined) and transdifferentiated. The phenomenon of transdetermination was discovered first in Drosophila development. It was found that mutants may cause fruit fly to develop a second pair of wings or grow legs instead of antennae on the head (Wang, 1990). We now know this is because of homeotic gene mutation. Eguchi and Okada demonstrated through clonal cell culture studies that retinal pigmented epithelial cells from chicken embryo at a late developmental stage can switch their cell type to those of lens cells, and develop lentoids (Eguchi and Okada, 1973).

In the normal development of any embryo, transitions between different cell types have to be occurred at some stages. At the blastula stage of an embryo, only single cell type proto-epithelium exists. All tissues and cells of adult are derived from this embryonic epithelia. The transition of proto-epithelium to primitive mesenchyme is the first and most important step in ontogenesis. During organogenesis, certain primitive mesenchyme may regain epithelial phenotype. For example, the highly proliferative mesenchyme of metanephric blastema is converted into primitive renal vesicle (epithelial structure). It is known the migratory neural crest cells in vertebrate embryo may differentiate into a large variety of derivatives, including the so-called mesectoderm, which plays a crucial role in the formation of connective and skeletal structures of the head.

Some fetal epithelia still retain the potential to change into mesenchymal cells. During development of the fetal palate, two palatal shelves fuse at the midline. Epithelial cells on each side of the fused area are converted into fibroblasts (Fitchet and Hay, 1989; Griffith and Hay, 1992).

In the adult body, transition between different types of epithelium may be a normal phenomenon. The superficial layer of the stratified squamous epithelium lining the mouse vagina changes cyclically into cuboidal mucinous cells in response to sex hormones secreted during the normal estrous cycle (Horvat et al., 1992). In pathological conditions, mature epithelial cells of one

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phenotype change into another, a process called epithelial metaplasia.

The members of the family of connective-tissue cells are related and to an unusual extent interconvertible. This family includes fibroblasts, fat cells, cartilage cells, bone cells and smooth muscle cells. Among them, fibroblasts seem to be the most versatile, displaying a remarkable capacity to differentiate into other members of the family.

In the adult body, epithelial and mesenchymal cells as derivatives of different germ layer autonomously maintain their respective character and pass it on to their respective progeny. That is to say, normal epithelium and mesenchyme cannot change into each other in vivo. Cell culture experiments demonstrate that even when cells are removed from their usual environment, they and their progenies generally remain true to their original instructions. Decidual stromal cells and fetal fibroblasts from skin, chorionic villi, and lung may express CK8,18 and 19 when cultured in either Condimed or Chang conditioned medium, but not in young or adult skin fibroblast cultures using the same cultured conditions (von Kaskull and Virtanen, 1987).

Traditionally, we used to think that during neoplastic transformation, cells do not change their state of commitment (determination), what is altered is the probability of a precursor cell proceeding down a predeterminal differentiation pathway. According to such view, the malignant neoplasms are described as a wide range of parenchymal cell differentiation, from those well- to those poorly- and to those completely un- or de-differentiated. However, it was suggested that transdetermination and then transdifferentiation should be recognized as another kind of differentiation disturbance in neoplasia, causing the tumor cells to express a phenotype different from that of their normal progenitor (Zhang and Xie, 1994).

Pathogenesis of cancer subtype

Cancers of various organs, which originate from the same cell, may comprise several subtypes with different histological characteristics and varied biological and clinical behavior. The possible cause of this heterogeneity has been investigated by several research groups recently. From the results of these investigations, we begin to understand that the different type of genetic instability may underlie the subtypes and predispose the tumors to different genetic alterations.

In their review, Pierotti et al. summarized genetic findings in the analysis of thyroid tumors: (1) Well-differentiated carcinomas of the papillary type are characterized by a high frequency of RTK (receptor tyrosine kinase) genes, RET and NTRK1 proto-oncogenes. In the majority of cases, intrachromosomal inversions of chromosome 10 and alteration of chromosome 1 activate RET and NTRK1 oncogenes respectively. (2) RAS point mutations are frequently observed in tumors with follicular histology. (3) The TP53 point mutation is detected almost exclusively in undifferentiated or anaplastic carcinomas (Pierotti et al., 1996).

Przygodzki et al. compared mutation type and rate of K-ras-2 and p53 gene in 22 pleomorphic (giant and spi ndle cell) carcinoma (PC), 42 squamous cell carcinoma (SqC) and 97 adenocarcinoma (AdC). K-ras-2 point mutations were not shown in SqC, whereas 9% and 36% frequency were found in PC and AdC respectively. 14% of PC had p53 point mutations, significantly fewer than did AdC (27%) or SqC (43%). The p53 mutation in PC was more common in exon 7, whereas those in SqC and AdC were more frequent in exon 8 (Przygodzki et al., 1996).

Lax et al. compared the frequencies of K-ras and p53 mutations and microsatellite instability between uterine endometrioid carcinoma (UEC) and uterine serous carcinoma (USC). The predominant genetic alteration in USC was p53 mutation, whereas MI and K-ras mutations were more common in UEC, with p53 mutations confined predominantly to a subset of high grade tumors (Lax et al., 2000).

Otis et al. investigated 34 ovarian epithelial tumors of different cell types and biological behavior for loss of heterozygosity (LOH) of tumor suppressor genes by PCR. Their results showed that LOH for TP53, D17S579/BRCA1 and ESR was frequent in ovarian serous cystadenocarcinomas (SCa), but was infrequent in clear cell carcinomas (CCa) and in serous tumor of low malignant potential (SLMP) (Otis et al., 2000).

To analyse phenotypic and genotypic changes in gastric cancer (GC), Wu et al. used CGH to assess global chromosomal aberrations. The results showed that gains on 8q and 17q, and losses on 3p and 5q were higher in intestinal GC than in diffuse GC; gains on 13q were more common in the diffuse type (Wu et al., 2001).

Günther et al. present a correlation analysis between the histological type of 19 invasive lobular carcinomas (LCs) and 29 invasive ductal carcinomas (DCs) and their unbalanced chromosomal aberrations using CGH. They found that the patterns of DNA gains and losses showed similarities in both groups, suggesting a common pathway of tumorigenesis; but LCs in comparison to DCs were characterized by higher frequencies for loss of 16q,17q and 22q and a lower incidence for gains of 8q and 20q (Günther et al., 2001).

In sum, these data suggest that different cytogenetic and/or molecular genetic pathways are involved in the pathogenesis of various subtypes of cancer. The variation of phenotype in histological subtypes results from neoplastic differentiation disturbances, including not only lower- to un-differentiation, but also transdifferentiation.

Transition between neoplastic epithelia and neuroendocrine cell

Now it is believed that neuroendocrine (APUD) cells are derivatives of two different systems, the neural crest

and endoderm. In an editorial, Andrews et al. (1998) drew attention to the conclusion that gut and pancreatic neuroendocrine cells arise from endoderm.

Whatever the origin be, the neoplastic epithelia and neuoendocrine cells may be converted to each other in some conditions. The same carcinoma cell may express both neuroendocrine and exocrine features, or exhibit glandular, squamous and neuroendocrine (McDowell and Trump, 1981; Hammer et al., 1992).

Experimental proliferation of hamster bronchial neuroendocrine cells may show squamous or exocrine as well as neuroendocrine differentiation (Gould, 1986). The cell type of metastatic tumor of the pulmonary neuroendocrine carcinoma may be squamous and/or glandular.

When only a single cell of clonalized human rectal adenocarcinoma was transplanted into a nude mouse or a single cell of clonalized rat intestinal adenocarcinoma was transplanted into a nude rat, they both grew to form tumors consisting of columnar, mucoid and neuroendocrinal cells (Cox and Pierce, 1982; Kirkland, 1988). Growth of cecal adenocarcinoma-derived cells on surfaces coated with a combination of type IV collagen and heparan sulfate proteoglycan resulted in both adhesion and induction of neuroendocrine characteristics. Neuroendocrine differentiation was found to be highly stimulated when cells were grown on intact, naturally occurring stroma (amniotic membranes, stripped colonic mucosa, fibroblast cells) (de Bruine et al., 1993).

Neuroendocrine cells are significantly more abundant in prostate cancer than in benign human prostate tissue and increase coordinate with progression of prostate cancer to advanced or hormone-resistant states. When the prostate cancer cells (LNCaP) are cultured by supplementation of cultures with interleukin 6 or in a medium deprived of steroid hormones, the cancer cells may change into NE-like phenotype. The experiment of Burchardt et al. showed that exposure of LNCaP cells to a hormone deficient medium drastically increased cyclic AMP production and this may identify the biochemical pathway through which hormone depletion induces a neuroendocrine conversion of prostate cancer cells (Burchardt et al., 1999).

Neoplastic epithelial-mesenchymal transition

When epithelia is converted into mesenchyme, the cells no longer express epithelial characteristics, such as cell polarity, cell adhesion molecules including cadherin, desmoplakin, catenin, and keratin containing intermediate filments. Instead, the cells acquire fibroblast-like properties.

Epithelial-mesenchymal transition occurs during tumor progression; i.e., invasion and metastasis of carcinoma cells. The malignant mesenchyme-like cells gain the potential to break through the basement membrane and invade the underlying mesenchyme.

Pathogenesis of neoplastic epithelial-mesenchymal transiiton (EMT)

Dedifferentiation

The process of transdifferentiation from retinal pigmented epithelial cells to lens cells passes through a dedifferentiated state. Such dedifferentiated cells showed no transcription of genes that are specific to either pigment cells or lens cells and had an increased expression of c-myc and high mitotic activity (Agata et al., 1993). In numerous instances, dedifferentiation is the essential prerequisite for epithelial-mesenchymal conversion. From the dedifferentiated state, the cells differentiate to another phenotype. This course is transcriptionally regulated and called redifferentiation.

Coexpression of cytokeratin and vimentin in carcinoma cell may be held as a transitional appearance from epithelial dedifferentiation to mesenchymal redifferentiation. Comparing the vimentin expression in renal cortical tubules or mammary epithelial cells of normal tissues, non-neoplastic hyperplastic lesions, benign tumors, and carcinomas, it was found that the dedifferentiation was associated with vimentin expression (Gould et al., 1990; Ward et al., 1992).

Effects of extracellular matrix molecules in EMT

Avian notochord epithelial cells, avian limb ectoderm and embryonic corneal epithelium, adult bovine corneal endothelium, and adult bovine or rodent thyroid follicles can be induced to form mesenchyme when suspended in 3D collagen gels (Hay, 1993). In this process, epithelial phenotypes, such as cytokeratin, cell junction and apical-based polarity, are lost in the elongated and vimentin-positive cells, i.e., fibroblasts, which emigrate from the former surface of the explant. When the cultured cell line NBT-II of a rat bladder carcinoma was attached to the collagen type I in the medium, or substitute for serum, ultroser G, was added to the medium, the cancer cell of epithelial type may be converted into the fibroblast type. If the inducing factors are removed, the epithelial phenotype may be restored (Boyer et al., 1989).

Effects of growth factors in EMT

The effects of differentiation, dedifferentiation and redifferentiation require a coordinated network that simultaneously controls cell growth and differentiation. Differentiation-induced cells progress through the G_0'-arrest cycle, whereby a certain population retains the capacity to de- and re-differentiation and reenter the cell cycle. In contrast, the rest of the differentiated population enters the irreversible G_0 phase (terminal commitment) that finally results in programmed cell death (Hass, 1994). By the receptor-mediated actions and via intracellular second messengers, growth factors stimulate the cells in the quiescent G_0 phase of the cell

cycle. When the transcription factors are activated, DNA synthesis is initiated and followed by cell division and dedifferentiation, or further redifferentiation.

Cultured neonatal rat hepatocytes (Pagan et al., 1996), mouse mammary gland epithelial cells (NMuMG) (Miettnen et al., 1994), nasophanryngeal carcinoma cells (CG-I) (Chen et al., 1994), and rat bladder carcinoma NBT-II cells (Valles et al., 1990) can all undergo an epithelial-mesenchymal transition, when the medium contains growth factor, such as EGF, TGF-alpha, -beta, or some subtypes of FGF. Within a few hours of the addition of nanogram quantities of these factors, the peripheral cells of NBT-II epithelial islands start to detach and migrate. Within 10-15 hours, all cells are converted into fibroblast-like cells. These changes are reversible by withdraw of the growth factors.

Expression of growth factor receptor may influence the regulation of E-cadherin-mediated cell adhesion. There is increasing experimental evidences to suggest that epidermal growth factor receptor tyrosine phosphorylation may lead to the inactivation of the E-cadherin/catenin complex in cancer cells through its interaction with beta- or gama-catenin in the cytoskeleton (Jawhari et al., 1999). Hypatocyte growth factor/scatter factor has been shown to produce similar effects of EGF, with phosphorylation of catenins (Crepaldi et al., 1994).

Piek et al. reported that TGF-beta-1 receptor and its effector, Smad proteins mediate the NMuMG epithelial to mesenchymal transition. Their experimental results showed that TGF-beta-1 strongly induced Smad2 phosphorylation and the nuclear accumulation of Smad2 and/or Smad3 (Piek et al., 1999). Bhowmick et al. demonstrated that TGF-beta rapidly activates RhoA-dependent signaling pathways in NMuMG epithelial cells to induce stress fiber formation and mesenchymal characteristics, and that blocking RhoA or its downstream target $p160^{ROCK}$, by the expression of dominant-negative mutants, inhibited TGF-beta mediated epithelial-to-mesenchymal transdifferentiation. The Rho family of small GTPases is regulator of the actin cytoskelaton and cadherin junction. Bhowmick et al. pointed out that TGF-beta-induced SMAD-mediated transcriptional activation may be dependent on RhoA activity (Bhowmick et al., 2001).

Dandachi et al. examined 128 breast carcinomas, and found a significant association between tenascin-C (TN-C) and vimentin (Vin) expression in cancer cells. TN-C expression also correlated positively with overexpression of c-erbB-2 oncoprotein and down-regulation of oestrogen receptors. TN-C is a large hexameric multidomain glycoprotein of the extracellular matrix (Dandachi et al., 2001).

Function of Ki-Ras oncogene and tumor-suppressor gene RB in EMT

Ellenriede et al. used TGF-beta to treat TGF-beta-responsive and nonresponsive pancreatic cancer cell lines with activating mutations of the Ki-ras oncogene. The role of the Ras-mitogen-activated protein kinase (MEK)-extracellular signal-regulated kinase (ERK) cascade in mediating TGF-beta-induced morphological and functional effects were studied by pretreatment with the MEK1 inhibitor PD98059 and by measuring ERK activation using immune complex kinase assays. In TGF-beta-responsive pancreatic cancer cells with activating Ki-ras mutations, TGF-beta treatment caused an epithelial-mesenchymal transdifferentiation with a more invasive phenotype. It is concluded that cross-talk with the Ras-MEK-ERK-signaling cascade appears to be essential for mediating these effects of TGF-betal (Ellenriede et al., 2001).

SV40 T antigen (LT) is an oncoprotein that inactivates nuclear regulators such as retinoblastoma (RB) family proteins and p53. Martel et al. showed that specific RB inactivation by LT induced dedifferentiation of nontumorigenic epithelial MDCK (Madin-Derby canine kidney) cells, which transformed into highly invasive fibroblastoid cells with the creation of a HGF/SF autocrine loop. These changes were concomitant with a massive apoptosis at high density and a strong down-regulation of c-myc. The stable retransformation of MDCK (LT) with a RB and/or c-myc-expressing vector may partially restored the expression of epithelial characteristics. These results indicated that two nuclear regulators, RB and/or RB-related proteins and c-myc, play a crucial role in regulating the plasticity of the epithelial phenotype in both normal and pathological situations (Martel et al., 1997).

Transition of carcinoma to carcinosarcoma

Recent years, the findings from comparative molecular analysis of the epithelial and mesenchymal components strongly supported monoclonal multidirectional histogenesis of carcinosarcomas. Those findings have all shown the carcinomatous and sarcomatous elements to share common genetic alterations (Thompson et al., 1996; Abein et al., 1997; Wada et al., 1997; Kounelis et al., 1998; Fujii et al., 2000). Generally, it is suggested that there is a single totipotential stem cell, which gives rise to the multiphasic appearance of carcinosarcoma. If this is true, the totipotential stem cell should coexist with tissue-determined specific stem cell that gives rise to carcinoma, then, how the great disparity in incidence between carcinoma and carcinosarcoma does occur.

We have known that the normal and neoplastic epithelial cell may be converted into mesenchyme, it is logically to deduce that the carcinosarcoma originate from transdifferentiation of carcinoma cell. In fact, clinically, the carcinoma may progress into carcinosarcoma. Some examples of pure endometrial carcinoma-carcinosarcomatous metastases conversion have been documented. One of them is a case of endometrial carcinoma that metastasized to the omentum

as a combination of carcinoma and rhabdomyosarcoma. The entire endometrium had been submitted for histologic examination and no sarcoma element was found (Sreenan and Hartn, 1995). Additionally, it was reported that carcinosarcoma may arise in duct papilloma of breast or sweat gland adenoma (Mckee et al., 1990; Pitt et al., 1995). In two cases of the 16 gynecological carcinosarcomas with homogeneous or heterogeneous patterns of LOH, Fujii et al. found the specific patterns of genetic progression to be consistent with sarcomatous components of the neoplasms arising from carcinomatous components (Fujii et al., 2000). When the cultured rat hepatocytes were transformed by methyl-nitro-nitroso-guanidine and then transplanted into homogenous rats, they grew up into each of the following tumor types: epidermoid carcinoma, glandular carcinoma, hepatocarcinoma, undifferentiated carcinoma, sarcoma, and carcinosarcoma (Tsao and Grishan, 1987).

Origin of pleomorphism in pleomorphic adenoma

Recently, Aigner et al. using histochemical methods, immunohistochemistry, and in situ hybridization to observe the extracellular matrix gene expression in pleomorphic adenoma, including epithelial- and mesenchymal-type mucopolysaccharides, cartilage typical glycosamino-glycans, CK, actin, Vim, S-100, collagen II, IV, X, laminin, and aggreecan core protein mRNA. For simultaneous detection of agreecan mRNA and cytokeratin polypeptides, in situ hybridization and subsequent immunohistochemistry were performed with double-labeling experiments. They found areas with unequivocal epithelial and mesenchymal differentiation in the tumor tissue. Many areas displayed a transitional phenotype with cells showing both epithelial and mesenchymal features. Their data provide evidence that in benign tumor the neoplastic epithelial cells transdifferentiate into mesenchymal cells (Aigner et al., 1998).

Neoplastic mesenchymal-epithelial transition

As mesenchyme transforms to epithelium, the intermediate filament is changed from vimentin to cytokeratin, and the non-polarized, loosely associated cells compact together to form polarized, closely associated cells. The compaction of cells is mediated by E-cadherin in a process that is mechanistically analogous to integrin mediated spreading of fibroblasts on an extracellular matrix substrate. It is suggested that the mechanism controlling E-cadherin activation in the mouse embryo probably involves alteration in the catenin cytoplasmic plaque protein, in the actin cytoskeleton, or in the interactions between them (Gumbiner, 1996). Birchmeir and Behrens (1994) pointed out that the endogenous E-cadherin promoter region is inaccessible in nonepithelial cells, then regulation of epithelial-specific expression of E-cadherin is largely due to specific suppression of promoter activity in non epithelial cells rather than specific activation in epithelial cells.

Expression of epithelial marker in normal and neoplastic mesenchyme

Neoplastic cells with coexpression of Vim and CK (and/or EMA) or expression of E-cadherin, or with epithelial-like morphology may be found in some primary mesenchymal tumors.

In cultures of vimentin positive, transformed mesenchymal cell lines, including SV40-transformed human fibroblasts, rhabdomyosarcoma, rat smooth muscle-derived cells, murine sarcoma and hamster BHK-2 cells, a small number of scattered cells were immunocytochemically positive for CK8 and 18. When the cultures of human SV80 fibroblasts were treated with 5-aza-c, the frequency of CK-positive cells increased significantly, but none of them turned positive to desmosomal proteins (Knapp and Franke, 1989).

Using the monoclonal antibody HECD-1, raised against the extracellular domain of E-cadherin, immunoreactivity was found in a minority of various soft tissue tumors, especially those with epithelioid features, including pleomorphic rhabdomyosarcomas, clear cell sarcomas, epithelioid sarcomas, synovial sarcomas and diffuse mesotheliomas (Sato et al., 1999).

Treatment with 5-aza-c induces the formation of a low proportion of CK8-containing intermediate filaments in murine fibroblastoidal or myoblastoidal cells derived from teratocarcinoma cells, with coexpression of CK18 and/or 19 in some of those cells. Rare stable cell lines of these display true epithelial morphology with typical desmosomes and CKs other than 8 and 18 (Semat et al., 1986).

Ela gene of adenovirus may act as a tumor suppressor gene in certain human tumor cell lines. Frish demonstrated that Ela expression partially convert several human tumor cells (rhabdomyosarcoma, fibrosarcoma, osteosarcoma, etc) and fibroblasts into an epithelial phenotype (Frisch, 1994).

Coexpression of the human Met receptor (met is an oncogene) and its ligand, HGF/SF, in NIH3T3 fibroblasts cause the cells to become tumorigenic in nude mice. Tsarfary et al. reported that the resultant tumors display lumen-like morphology, contain carcinoma-like focal areas with intercellular junctions resembling desmosomes, and coexpress CK and Vim (Tsarfary et al., 1994).

Synovial sarcoma—Real carcinosarcoma

Synovial sarcoma should be identifies as a kind of carcinosarcoma or carcinoma of mesenchymal tissue (Chadially, 1987). The spindle cell type monophasic, biphasic, and glandular type monophasic synovial sarcoma may be regarded respectively as sarcoma, carcinosarcoma and carcinoma in the differentiation

spectrum of this neoplasm.

A characteristic translocation t(x;18) (p11;q11) is seen in almost all synovial sarcoma with informative karyotypes. The translocation fuses the SYT gene from chromosome 18 to either of highly homologous genes at Xp11, SSX1 and SSX2, located in the vicinity of omithine aminotransferase-like (OATL) pseudogenes 1 and 2, respectively. The encoding SYT-SSX chimeric proteins are thought to be involved in the transcriptional deregulation of certain tumorigenic target genes.

Kawai et al. (1998) and Antonescu et al. (2000) analyzed SYT-SSX fusion transcripts in 45 and 73 synovial sarcomas, respectively, and compared the results with relevant clinical and pathological data. Both of them found a strong association of SYT-SSX fusion transcript type with the histologic subtype and confirmed earlier FISH results from three independent studies including a total of 23 tumors.

The report by Antonescu et al. indicate that the monophasic types of synovial sarcoma (with SYT-SSX2) have a significantly higher ki-67 labeling index than biphasic types (with SYT-SSX1), however, apoptosis was rarely observed in either type, consistent with prominent expression of the anti-apoptosis protein bcl-2 in almost all cases. The bcl-2 protein expression was strong in spindle cells in contrast to the weak or negative reactivity observed in epithelial cells. Bcl-2 positive spindle cells consistently surrounded the negative epithelial elements, a pattern confirmed by the studies of Antonescu et al. and other investigators. The spindle and adenomatous elements in biphasic synovial sarcoma may be analogous to the undifferentiated and well-differentiated elements of carcinoma, confirming that bcl-2 protein expression is indeed different between two areas of the biphasic tumor (Antonescu et al., 2000).

Other kinds of carcinosarcoma or carcinoma occuring in the mesenchymal tissue

Epithelioid sarcoma

Epithelioid sarcoma may be hypothesized as a type of mesenchymal carcinoma with simple epithelium differentiation. Electron microscopic figures of the tumor showed a spectrum of cellular differentiation from fibrohistiocytic cells to epithelial-type cells with junctions, microvilli, and tonofilaments. All the tumors display both vimnetin and epithelial markers, just like some poorly differentiated carcinoma cells. In some cases the tumor cells may coexpress neurofilament protein, NES, or even synaptophysin (Gerharz et al., 1990).

Malignant mesothelioma

The regenerating mesothelium may originate from either the surrounding uninjured mesothelial cell population or the subserosal cells. It is suggested that the subserosal cell is distinct from other connective tissue cells in its ability to coexpress vimentin and cytokeratin, and serves as the replicated cell which can differentiate into surface epithelium (Bolen et al., 1986). Malignant mesothelioma originates from subserosal mesenchymal cell. As its normal progenitor possesses bidifferentiated potential, this tumor may show a differentiation spectrum from sarcoma to carcinosarcoma and carcinoma.

Adamantinoma of long bone

Adamantinoma of long bone composed of epithelial and fibrous components is closely related to osteofibrous dysplasia (OFD). Hazelbag et al. studied the immunoreactivity of collagens I, III, and IV, fibronectin, laminin, and tenascin in the fibrous and epithelial components of 21 adamantinoma tissue, comparing with 3 synovial sarcomas. They found: (a) focal densities of basement membrane substances in OFD-like areas with keratin-positive cells, (b) increase of basement membrane continuity with gain of histological distinction between epithelial and fibrous components, and (c) strong tenascin reactivity directly surrounding well-developed epithelial fields, with weaker staining more distantly. This is in analogy to the synovial sarcoma. Hazelbag et al. suggested that the epithelial component in adamantinoma maybe transformed directly from the osteofibrous tissue (Hazelbag et al., 1997).

Non-neuroectodermal tumors with neural or melanocytic phenotype

The expression of "neural" markers does not signify a neuroectodermal origin. For example, although normal mesenchyme does not express neural differentiation, but "neural" markers may be found in mesenchymal tumors. Synovial sarcoma may be immunohistochemically positive for neurofilament 68kd, S-100, NSE, Leu-7 and GFAP (Noguera et al., 1998); epithelioid sarcoma cells express neurofilament, NSE and synaptophysin protein (Gerharz et al., 1990); MFHs show neurofilament and neural associated antigen positive (Lawson et al., 1987). Molenaar and Muntinghe studied the expression of neural cell adhesion molecules (N-CAM) and neurofilament protein isoforms, they found that both neural markers express in rhabdomyosarcoma, leiomyosarcoma, fibrosarcoma, MFH, malignant rhabdoid tumor and fibromatousis; and N-CAM positive in synovial sarcoma (Molenaar and Muntinghe, 1999). The desmoplastic small round cell tumors (DSRCT) may show positive staining with antibodies to NES, Leu-7 and other neural antigens; which is more possible to originate from mesenchymal tissue, such as subserosal cells (Ordónez, 1998).

Origin of Ewings' sarcoma

Ewings'/pPNET (Ewings' sarcoma/peripheral primitive neuroectodermal tumor) form a family of bone

and soft tissue tumors in which typical Ewings' sarcoma with mere mesenchymal phenotype lies at one end of the differentiation spectrum and pPNET with clear evidence of neural marker at the other end. Lichtenstin and Jaffe (1947) suggested that the origin of Ewings' sarcoma is mesenchymal or primitive form of connective tissue. Currently, because the ES cells may be induced in virtro to express neural markers, numerous pathologists prefer to support the view on origin of Ewings'/pPNET from neural crest cell, which, as neuroblastoma, belongs to pPNET category (Dehner, 1993).

Neuroblastoma originates from the sympatho-adrenal lineage of the neural crest, but, the primary location of most Ewings'/pPNET unrelated any specific structure of the nervous system. The characteristic chromosome changes of neuroblastoma are deletion of 1p36.2-3, amplification of the proto-oncogene MYCN and abnormalities of the chromosome number (McManus et al., 1996). The special cytogenitic aberration of Ewings'/pPNET is chromosomal translocation resulting in gene fusion. One of the criterions for diagnosing classic neuroblastoma is the presence of Homes-Wright pseudorosettes. However, the number of rosettes in pPNETs is usually described by most reporters as a few or occasional (Dehner, 1993). The differentiation-potential of neuroblastoma shows neural mono-direction. Ewings'/pPNET shows multi-differentiation and may overlap somewhat in appearance with DSRCT, or even alveolar rhabdomyosarcoma, both of which also show characteristic chromosome translocation. From these points, Ewings'/pPNET is more close to non-neural derived tumor in phenotypes and cytogenetics. The discovery of hybrid tumor comprising Ewings'/pPNET and DSRCT further demonstrated that the DSRCT and pPNET possibly share a common histogenesis (Katz et al., 1997).

Fukunaga et al. reported a case of carcinosarcoma with neuroectodermal differentiation occurred in the uterus of a 54-year-old woman. The neoplastic elements include squamous carcinoma, leiomyosarcoma and islands of small- to medium-sized cells with rosette-like formation and immunoreactivity for GFAP, Leu-7, NSE and synaptophysin (Fukunaga et al., 1996). Certainly, in this case the cells with neural differentiation did not arise from neural crest cell.

Ewings'/pPNET is characterized by the special chromosomal translocation resulting in a fusion gene and its encoding chimeric protein. In at least 90% of Ewings'/pPNET, the translocation is t(11;22) (q24;q12), resulting in the fusion of parts of the EWS gene with parts of the FLI-1 gene encoding for transcription factor. In the encoded chimeric protein, the aminoterminal EWS domain is linked to the DNA-binding domain of the transcription factor. Another 5% of cases, t(21;22) (q22;q12) is present, which involves EWS and ERG gene. Another rare translocation is t(7;22) (p22;q12), resulting in EWS/ETV-1. FLI-1, ERG and ETV-1 all belong to protooncogen ETS family (Ladanyi, 1995).

EWS/FLI-1 (or EWS/ERG, ETV-1) is a transcription factor. EWS/FLI-1 efficiently transformed NIH3T3 cells, but FLI-1 did not. Experiments with EWS/FLI-1 deletion mutants indicated that both EWS and FLI-1 domains are necessary for transformation by the t(1;22) translocation product (May et al., 1993a,b). Recently, Teitell et al. reported that NIH3T3 fibroblasts infected with either EWS/FLI-1 or EWS/ETV-1 resembled small round cell tumor microscopically, and showed both epithelial and neuroectodermal phenotypes which represented by CK15 expression, dense junction, and neurosecretory granule formation. The altered cells lost both extracellular collagen deposition and RER, which means loss of mesenchymal differentiation (Teitell et al., 1999).

Although all the Ewings'/pPNET harbor an identical model of chromosomal translocation, but its differentiated spectrum includes mesenchymal phenotype at one end, and neural at the other. Other small cell tumors of soft tissue, such as DSRCT, polyphenotypic tumors, even a few cases of alveolar or embryonal rhabdomyosarcoma, may also posses t(11;22) (q24;q12) and EWS/FLI-1 fusion gene (Sorensen et al., 1995; Thorner et al., 1996). From these findings, we may deduce that the expression of neural phenotype in Ewings'/pPNETs is not merely decided by the formation of EWS/FLI-1 or EWS/ERG fusion gene but also required the activation of certain genes related to neural differentiation.

EWS-FLI-1 fusion gene may be classified as type 1 (fusion between EWS exon 7 and FLI-1 exon 6) and type 2 (fusion between EWS exon 7 and FLI-1 exon 5). Amann et al. investigated Ewings' family of tumors in terms of a possible correlation between the type of EWS chimeric transcripts and reactivity with the neuroglial markers (NgM), including polyclonal and monoclonal NSE, S-100, chromogranin A, synaptophysin, Leu-7, GFAP and neurofilament. No NgM expression was found in 16/30 (53%) cases of type I, compared with on 2 of 11 (18%) in type II. For tumors with at least 1 NgM, 14 of 30 (47%) cases are present in type I, and 9 of 11 (82%) in type II. The data suggested that the length of the involved segment of the FLI-1 gene directly influenced the extent of neural differentiation (Amann et al., 1999).

In conclussion, neuroblastomas may be deduced logically being derived from neural tissue. Ewings'/pPNET should be hypothesized to arise from mesenchymal tissue.

Vasoactive intestinal peptide (VIP) is a neuromodulator that regulates both proliferation and differentiation of neuronal precursor. Frühwald et al. analyzed cPNET cell lines, cPNET tumor and Ewings'/pPNET, using reverse transcriptase-polymerase chain reaction and Southern hybridization. They found that VIPR1 and VIPR2 are more highly expressed in both primary cPNET tumors and cPNET cell lines. This result may reflect the divergent pathways of cPNET toward neural differentiation and Ewings'/pPNET to mesenchymal cells (Frühwald et al., 1999). The question is how such divergent pathways of differentiation occur. A more reasonable reply is that the origin of cPNET is

distinct from that of pPNET, the former from neural tissue, and the latter from mesenchymal cells.

Origin of clear cell sarcoma

Clear cell sarcoma (CCS) is almost invariably deep seated and intimately associated with tendons, aponeuroses and fasia, rarely being located elsewhere. Yokoyama et al. reported a primary CCS of bone, arising in the ulna (Yokoyama et al., 1996). The CCS cells may produce melanin, and immunohistochemically are positive for S-100 protein, HMB-45 and vimentin. Sometimes small amount of low molecular weight cytokeratins may be expressed. Ultrastructurally, the tumor cells form melanosomes. Since CCS displays melanocytic phenotypes, and melanocyte is not kown to appear in tendons and aponeuroses, it is also named melanoma of soft parts derived from neural crest.

Approximately 75% of clear cell sarcomas and all of the cultured cell lines harbor a special chromosome translocation, t(12;22) (q13; q12) (Graadt van Roggen et al., 1998). It is said that the molecular translocations of this region may be detected in more cases by more sensitive techniques of FISH and RT-PCR than by karyotype analysis (Sonobe et al., 1999). In addition, abnormalities in the copy number of chromosome 7 and 8 have been revealed in ~50% and ~60% cases, respectively (Graadt van Roggen et al., 1998). The t(12;22) does not occur in cutaneous melanoma. Most karyotypic abnormalities of cutaneous melanoma (MM) occur in chromosome 1, 2, 3, 5, 6, 7, 9 and 11. These significant cytogenetic differences of CCS and MM strongly indicate that in histogenesis CCS is a separate entity distinct from MM. Additionally, in view of its soft part location, it is reasonably deduced that CCS originates from mesenchymal cell.

The breakpoints of the t(12;22) of CCS have been identified at the molecular level. On chromosome 22, the EWS gene, originally cloned from the t(11;22) translocation of Ewings'/pPNET, is involved. The ATF-1 gene is rearranged on chromsome 12. A fusion mRNA transcript is thereby produced, in which the RNA-binding domain of EWS is replaced by the DNA-binding domains of ATF-1. Two hybrid transcripts are documented, including the EWS aa 1-325 with the ATF-1 aa 65-271 and the EWS aa 1-349 with the ATF-1 aa 110-271. The functional consequences of this gene fusion may be similar to those of other translocations involving EWS, but the target gene is determined by the DNA-binding specificity of the ATF-1 component of the chimeric gene. Considering the experience of comparable genetic events in other sarcoma groups, Graadt van Roggen et al. assumed that t(12;22) and the regular appearance of abnormalities of chromosome 7 and 8 play an important role in the pathogenesis of CCS (Graadt van Roggen et al., 1998).

Melanocytic phenotype expressing in carcinoma

Primary cutaneous, mucosal and some visceral melanomas are the malignant tumor of melanocytes. It is believed that the melanin-producing cells, derived from the neural crest, may migrate throughout the body during embryological development. This theory is supported by the facts that benign melanocytes and melanocytic proliferations have been identified in mucosa of some sites and some visceral organs. However, from a few reports, we can also find that, in rare instances, carcinoma may express melanocytic differentiation.

Cohen et al. reported a pulmonary blastoma with areas of melanocytic differentiation indistinguishable from malignant melanoma (Cohen et al., 1990). Padmore et al. reported two cases of primary breast tumors with admixture of pigmented malignant melanoma and ductal carcinoma (Padmore et al., 1996). In both cases, ductal carcinoma in situ was identified, and double-labeling immunohistochemistry showed CK positive for carcinoma cells, HMB45 positive for melanoma cells and S-100 positive for both components. Electron microscopy demonstrated melanosomes and premelanosomes in the melanoma components. The authors believed these two cases being monoclonal origin with bidirectional differentiation. These authors cited literatures to demonstrate that there are other reports describing six tumors with features of both melanoma and carcinoma. Among these cases, three cases of combined melanoma and squamous cell carcinoma showed intimate intermingling of the two components.

Nobukawa et al. reported the fourth primary breast tumor with a combination of malignant melanoma and ductal carcinoma (Nobukawa et al., 1999). The in situ component of the carcinoma was identified in the primary tumor. Metastases in the lympho nodes and thoracic spinal bone marrow showed a dual tissue structure of carcinoma and melanoma. One of the metastatic tumors in the lung consisted of only the melanoma component. Microsatellite analysis showed the same genetic alterations with loss of heterozygosity on chromosome arms 1p, 3q, 4q, 9q, 10q, 13q, 16q, 17p, and 17q in in situ, invasive and metastatic foci. Nobukawa et al. concluded that the carcinoma and melanoma components were of the same clonal origin and that the breast carcinoma might have diverged to aberrant malignant melanoma during the early period of carcinoma progression.

Histogenesis of MFH

Malignant fibrohistiocytoma (MFH) is composed of fibroblast-like cells, histiocyte-like cells and their intermediate type (Enjoji et al., 1980; Hoffman and Dickersin, 1983).

Heterogeneity of MFH

1. Fibroblast origin:

Comparing MFH in man with that in animals, Schneider et al. concluded that MFH originates from a

primitive mesenchymal stem cell, fibroblastoid cell and fibroblast (Schneider et al., 1999). This theory was supported by a lot of evidences as follows: The MFH cells expressed mesenchymal antigens (Roholl et al., 1985a,b; Iwasaki et al., 1992). Injection of DMBA into the knee joint cavity of rats may induce MFHs and fibrosarcomas or synovial sarcomas in and around the joint (Ghadially and Roy, 1966; Sakamoto, 1986). After several recurrences, fibrosarcoma may transform into MFH (Katenkamp and Neupert, 1982). Fibrosarcoma cells (RFS) derived from a cadium induced fibrosarcoma of rat and RFS-cells in different subcultures produced MFH and fibrosarcoma in nude mice and baby rats (Katenkamp and Neupert, 1982). Nontransformed and transformed fibroblast-like mouse embryo cells can be induced to differentiate into macrophages or histiocytes in a medium supplemented with human plasma (Krawisz et al., 1981). These findings demonstrated that the histiocyte-like cells could result from transdifferentiation of neoplastic fibroblasts.

Osanai et al. reported the existence of diploid fibrohistiocytoid (FH) cells in various chronic inflammatory tissues. These cells are metamorphosed fibroblasts. From the findings of a recent study, Osanai et al. Suggested that the FH cells have a possibility of neoplastic potential for the development of MFH in mice (Osanai et al., 2000).

Histiocyte origin

The main supporting evidence is the experiment of Yumoto and Murimoto. They inoculated SV40-transformed bone marrow macrophages in syngeneic mice to produce a transplantable tumor. The tumor was composed of spindle cells with arrangement in storiform and function as histiocyte-like and fibroblast-like cells (Yumoto and Morimoto, 1980). This experiment demonstrated that MFH may be derived from transdifferentiation of histiocytes. In addition, some authors reported that MFH express antigenic markers specific for monocytes-macrophages (Shirasuna et al., 1985; Strauchen and Dimitriu-Bona, 1986; Binder et al., 1992).

Other origins

The dedifferentiated components of dedifferentiated sarcoma (e.g. dedifferentiatiated liposarcoma, dedifferentiated chondrosarcoma and dedifferentiated leiomyosarcoma) and sarcomatous cells of carcinosarcoma e.g. sarcomatous carcinoma of lung, kidney and prostate, and carcinosarcoma of breasts usually look like MFH or fibrosarcoma (Snover et al., 1982; Bertoni et al., 1987; Ro et al., 1987, 1992; Wargotz and Norris, 1989; Hashimoto et al., 1990; Meis, 1991; Shannon et al., 1992; Nakajima et al., 1999). In addition, the individual case of malignant melanoma, gliosarcoma and malignant lymphoma, microscopically or even electron-microscopically, may seem to be in accordance with the appearance of MFH (Blom et al., 1983; Chan et al., 1990; Ng and Poon, 1990).

Karyotype progression of MFH

The karyotype of MFH is far more complex than that of fibrosarcoma. The cytogenetical evidence of clonal evolution has been found in some tumors (Orndal et al., 1994). A greater part of the tumors were near triploid or near tetraploid, some were hyperdiploid even hypodiploid (Donner, 1994). The tumors develop through the acquisition of structural aberrations and chromosome loss or through gain of chromosome (Mandahl et al., 1989). Ring, dicentric and telomeric association chromosomes seem to represent early events in the development of MFH (Mandahl et al., 1988; Orndal et al., 1992, 1994). Sometimes, ring chromosome is the sole cytogenetical aberration of myxoid MFH (Mandahl et al., 1988; Orndal et al., 1992), and also the sole consistent chromosome alteration of well-differentiated liposarcoma and dedifferentiated liposarcoma, of which the dedifferentiated area is commonly composed of MFH elements (Fletcher et al., 1996, 1999; Rosai et al., 1996). These may be the evidences to support the view that pleomorphic MFH results from tumor progression.

Genberg et al. established two cell lines from two subsequent recurrences of MFH. with identical marker chromosomes in common. The U-2149 cell line from the second recurrence consisted of mainly fibroblast-like cells and was in the hypotriploid region. The U-2197 cell line from the third recurrence was composed of mainly histiocyte-like cells and in the penta-hexaploid region. The marker M18 in U-2197 represented a marker 20 in U-2149 subjected to superimposed structural rearrangements. According to their data, Genberg et al. explained the appearance of histiocyte-like cells in MFH as a consequence of chromosomal progression (Genberg et al., 1989).

Pilotti et al. investigated p53 and mdm2 overexpression in 98 lipomatous tumors by immunocytochemistry and, in part, by molecular and cytogenetic analysis. Among the 74 cases of liposarcomas, 14 cases were dedifferentiated subtype, in which, the differentiated component was well-differentiated, while the dedifferentiated area had MFH features in 13 cases. The results show that in the retroperitoneal well-differentiated-dedifferentiated group, MDM2-mediated inactivation of p53 could be related to the pathogenetic mechanism, in the non-retroperitoneal WD-DD group, the TP53 mutations appear to correlate with the dedifferentiation process (Pilotti et al., 1997). Hisaoka et al. studied eight cases of dedifferentiated liposarcoma with myxoid MFH myxoid areas. The clinicopathologic, cytogenetical and molecular features showed that the differentiated part of tumors was more closely related to well-differentiated liposarcoma rather than to ordinary myxoid liposarcoma, and the dedifferentiated part was myxoid MFH. The

myxoid portions frequently showed a higher proliferative activity and more mdm2 and p53-positive tumor cells than in well-differentiated areas. Hisaoka et al. claimed that an altered p53 pathway, including p53 gene mutations and mdm2-mediated inactivation of p53 may play a role in tumorigenesis of this myxoid subtype of liposarcoma and its progression (dedifferentiation) to change into myxoid MFH (Hisaoka et al., 1999).

Conclusion

Differentiation disturbance of cancer cells should include not only undifferentiation and dedifferentiation, but also transdifferentiation. The pathogenesis and progression of neoplasm are closely in association with genetic instabilities, including subtle sequence changes, alteration in chromosome number, chromosome translocation and gene amplifications (Lengauer et al., 1998). Genetic instablities are the basis of neoplastic dedifferentiation and transdifferentiation. The pathogenesis of cancer subtypes, neoplastic epithelial-neuroendocrine conversion and neoplastic epithelial-mesenchymal transition may be simply the result of subtle sequence changes and alteration in extracellular matrix molecules or stimulation by growth factors, via regulation of cell proliferation, differentiation and programmed cell death. Chromosomal translocation cause enforced expression of oncogenes located near the breakpoints or result in tumor-specific fusiom proteins. The genes at translocation junctions are often transcription factors, normally involved in developmental processes (Rabitts, 1999). As to neoplastic mesenchymal-epithelial transition in synovial sarcoma and mesenchymal-neural transdifferentiation in the Ewings'/pPNET and clear cell sarcoma, chromosome translocations (gene rearrangements) are crucial not only for tumorigenic effect, but also for neoplastic transdifferentiation.

It had been debated for decades about the morphogenesis of some groups of neoplasms. These include (a) the histological subtype, (b) multidirectional differentiation tumors, (c) tumors with the characteristic phenotype of a certain tissue occurring in an organ foreign to such tissue, e.g. meningioma in lung, (d) tumors with a phenotype dissimilar to any type of normal tissue, e.g. alveolar soft part sarcoma. The histological appearances of these tumors may result from transdifferentiation of certain neoplastic cells, and their histogenesis may be resolved at the cytogenetical and molecular levels.

References

Abein E.C., Smit V.T., Wessels J.W., De Leeuw W.J.F., Cornelisse C.J. and Fleuren G.J. (1997). Molecular genetic evidence for the conversion hypothesis of the origin of malignant mixed mullerian tumours. J. Pathol. 183, 424-31.

Agata K., Kobayashi H., Itoh Y., Mochii M., Sawada K. and Eguchi G. (1993). Genetic characterization of the multipotent dedifferentiated state of pigmented epithelial cells in vitro. Development 118, 1025-1030.

Aigner T., Neureiter D., Volker U., Belke J. and Kirchner T. (1998). Epithelial-mesenchymal transdifferentiation and extracellular matrix gene expression in pleomorphic adenomas of the parotid salivary gland. J. Pathol. 186, 178-185.

Amann G., Zoube A., Salzer-Kuntschik M., Windhager R. and Kovar H. (1999). Relation of neuroglial marker expression and EWS gene fusion types in MIC2/CD99-positive tumors of the Ewing family. Hum. Pathol. 30, 1058-1064.

Andrew A., Kramer B. and Rawdon B.B. (1998). The origin of gut and pancreatic neuroendocrine (APUD) cell - The last word? J. Pathol. 186, 117-118.

Antonescu C.R., Kawai A., Leung D.H., Lonardo F., Wooddruff J.M., Healey J.H. and Ladanyi M. (2000). Strong association of SYT-SSX fusion type and morphologic epithelial differentiation in synovial sarcoma. Diagn. Mol. Pathol. 9, 1-8.

Bertoni F., Ferri C., Benati A., Bacchini P. and Corrado F. (1987). Sarcomatoid carcinomas of the kidney. J. Urol. 137, 25-28.

Bhowmick N.A., Ghiassi M., Bakin A., Aakre M., Lundquist C.A., Engel M.E., Arteage C.L. and Moses H.L. (2001). Transforming growth factor-beta1 mediates epithelial to mesenchymal transdifferentiation through a RhoA-dependent mechanism. Mol. Biol. Cell 12, 27-36.

Binder S.W., Said J.W., Shintaku P. and Pinkus G.S. (1992). A histiocyte-specific marker in the diagnosis of malignant fibrous histiocytoma. Use of monoclonal antibody KP-1 (CD68). Am. J. Clin. Pathol. 97, 759-763.

Birchmeier W. and Behrens J. (1994). Cadherin expression in carcinoma: Role in the formation of cell junction and the prevention of invasiveness. Biochem. Biophys. Acta 198, 11-26.

Blom P.G., Stenwig A.E., Sobel H.J. and Johannessen J.V. (1983). Intriguing cases. Case 6. Ultrastruct. Pathol. 5, 307-313.

Bolen J.W., Hammar S.P. and McNutt M.A. (1986). Reactive and neoplastic serosal tissue. A light-microscopic, ultrastructural, and immunocytochemical study. Am. J. Surg. Pathol. 10, 43-47.

Boyer B., Tucker G.C., Valles A.M., Gavrilovic J. and Thiery J.P. (1989). Reversible transition towards a fibroblastic phenotype in a rat carcinoma cell line. Int. J. Cancer Suppl. 4, 69-75.

Burchardt T., Burchardt M., Chen M-W., Cao Y., dela Taille A., Shabsigh A., Aayek O., Dorai T. and Buttyan R. (1999). Transdifferentiation of prostate cancer cells to a neuroendocrine cell phenotype in vitro and in vivo. J. Urol. 162, 1800-1805.

Chadially F.N. (1987). Is synovial sarcoma a carcinosarcoma of connective tissue? Ultrastruct. Pathol. 11,147-151.

Chan J.K.C., Buchanan R. and Fletcher C.D.M. (1990). Sarcomatoid variant of anaplastic large-cell Ki-1 lymphoma. Am. J. Pathol. 14, 983-986.

Chen J.K., Shen L.S., and Chao H.H. (1994). Correlation of transformation from epithelial to mesenchymal-like morphology and endogenous bFGF levels in human nasopharyngeal carcinoma cells. J. Cell. Physiol. 160, 401-408.

Cohen R.E., Weaver M.G., Montenegro H.D. and Abdul-Karim F.W. (1990). Pulmonary blastoma with malignant melanoma component. Arch. Pathol. Lab. Med. 114, 1076-1078.

Cox W.F. and Pierce G.B. (1982). The endodermal origin of the endocrine cells of an adenocarcinoma of the colon of the rat. Cancer 50, 1530-1538.

Crepaldi T., Pollack A.L., Part M., Zborek A., Mostov K. and Comoglio P.M. (1994). Targeting of the SF/HGF receptor to the basolateral

domain of polarized epithelial cells. J. Cell Biol. 125, 313-320.

Dandachi N., Hauser-Kronberger C., Moré E., Wiesener B., Hacker G.W., Dietze O. and Wirl G. (2001). Co-expression of tenascin-C and vimentin in human breast cancer cells indicates phenotypic transdifferentiation during tumour progression: correlation with histopathological parameters, hormone receptors, and oncoproteins. J. Pathol. 193, 181-189.

de Bruine A.P., Dinjens W.N.M., Van Den Linden E.P.M. Pijis M.M.J., Moerkerk P.T. and Basman F.T. (1993). Extracellular matrix components induce endocrine differentiation in vitro in NCL-H716 cells. Am. J. Pathol. 142, 773-782.

Dehner L.P. (1993). Primitive neuroectodermal tumor and Ewing's sarcoma. Am. J. Surg. Pathol. 17, 1-13.

Donner L.R. (1994). Cytogenetics of tumors of soft tissue and bone. Cancer Genet. Cytogenet. 78, 115-126.

Eguchi G. and Okada T.S. (1973). Differentiation of lens tissue from the progeny of chick retinal pigment cells cultured in vitro: A demonstration of a switch of cell type in clonal cell culture. Proc. Natl. Acad. Sci. USA 70, 1495-1499.

Ellenrieder V., Hendler S.F., Boeck W., Seufferlein T., Menke A., Ruhland C., Adler G. and Gress T.M. (2001). Transforming growth factor beta1 treatment leads to an epithelial-mesenchymal transdifferentiation of pancreatic cancer cells requiring extracellular signal-regulated kinase 2 activation. Cancer Res. 61, 4222-4228.

Enjoji M., Hashimoto H., Tsuneyoshi M. and Iwasaki H. (1980). Malignant fibrous histiocytoma. A clinicopathologic study of 130 cases. Acta. Pathol. Jpn. 30, 727-741.

Fitchet J.E. and Hay E.D. (1989). Medial edge epithelium transforms to mesenchyme after embryonic palatal shelves fuse. Dev. Biol. 131, 455-474.

Fletcher C.D.M., Akerman M., Cin P.D., de Wever I., Mandahl N., Mertens F., Mitelman F., Rosai J., Rydholm A., Sciot R., Tallini G., Van Den Berghe H., Van De Ven W., Vanni R. and Willen H. (1996). Correlation between clinicopathological features and karyotype in lipomatous tumors. A report of 178 cases from the chromosomes and morphology (CHAMP) collaboratative study group. Am. J. Pathol. 148, 623-629.

Fletcher C.D.M., Cin P.D., de Wever I., Mandahl N., Mertens F., Mitelman F., Rosai S., Rydholm A., Sciot R., Tallini G., Van Den Berghe H., Vanni R. and Willen H. (1999). Correlation between clinicopathological features and karyotype in spindle cell sarcomas. A report of 130 cases from the CHAMP study group. Am. J. Pathol. 154, 1841-1847.

Frisch S.M. (1994). Ela induces the expression of epithelial characteristics. J. Cell Biol. 127, 1085-1096.

Frühwald M.C., O'Dorisio M.S., Fleitz J., Pietsch T. and Reubi C. (1999). Vasoactive intestinal peptide (VIP) and VIP receptors: gene expression and growth modulation in medulloblastoma and other central primitive neuroectodermal tumors of childhood. Int. J. Cancer 81, 165-173.

Fujii H., Yoshida M., Gong Z.X., Matsumoto Y., Hamano Y., Fukunaga M., Hruban R.H., Gabrielson E. and Shirai T. (2000). Frequent genetic heterogeneity in the clonal evolution of gynecological carcinosarcoma and its influence on phenotypic diversity. Cancer Res. 60, 114-120.

Fukunaga M., Nomura K., Endo Y., Ushigome S. and Aizawa S. (1996). Carcinosarcoma of the uterus with extensive neuroectodermal differentiation. Histopathology 29, 565-570.

Genberg M., Mark J., Hakalius L., Ericsson J. and Nister M. (1989). Origin and relationship between different cell types in malignant fibrous histiocytoma. Am. J. Pathol. 135, 1185-1196.

Gerharz C.D., Moll R., Ramp U., Mellin W. and Gabbert H.E. (1990). Multidirectional differentiation in a newly established human epithelioid sarcoma cell line GRU1 with coexpression of vimentin cyto-keratin and neurofilament proteins. Int. J. Cancer 45, 143-152.

Ghadially F.N. and Roy S. (1966). Experimentally produced synovial sarcomas. Cancer 19, 1901-1908.

Gould V.E. (1986). Histogenesis and differentiation. A re-evaluation of these concepts as criteria for the classification of tumors. Hum. Pathol. 17, 212-215.

Gould V.E., Koukoulis G.K., Jansson D.S., Nagle R.B., Franke W.W. and Moll R. (1990). Coexpression patterns of vimentin and glial filament protein with cytokeratins in the normal, hyperplastic and neoplastic breast. Am. J. Pathol. 137, 1143-1156.

Graadt van Roggen J.F., Mool W.J. and Hogendoorn P.C.W. (1998). Clear cell sarcoma of tendons and aponeuroses (malignant melanoma of soft parts) and cutaneous melanoma: Exploring the histogenetic relationship between these two clinicopathological entities. J. Pathol. 186, 3-7.

Griffith C.M. and Hay E.D. (1992). Epithelial-mesenchymal transformation during palatal fusion: Carboxyfluorescein traces cells at light and electron microscopic levels. Development 116, 1087-1099.

Gumbiner B.M. (1996). Cell adhesion: The molecular basis of tissue architecture and morphogenesis. Cell 84,345-357.

Günther K., Merkelbach-Bruse S., Amo-Takyi B.K., Handt S., Schröder W. and Tietze L. (2001). Differences in genetic alterations between primary lobular and ductal breast cancers detected by comparative genomic hybridization. J. Pathol. 193, 40-47.

Hammer S.P., Insalaco S.J. and Lee R.B. (1992). Amphicrine carcinoma of the uterine cervix. Am. J. Clin. Pathol. 97, 516-522.

Hashimoto H., Daimura Y., Tsuneyoshi M. and Enjoji M. (1990). Soft tissue sarcoma with additional anaplastic components. A clinicopathologic and immunohistochemical study of 27 cases. Cancer 66, 1578-1589.

Hass R. (1994). Retrodifferentiation and cell death. Crit. Rev. Oncogenesis 5, 359-371.

Hay E. (1993). Extracellular matrix alters epithelial differentiation. Curr. Opi. in Cell Biol. 5, 1029-1035.

Hazelbag H.M., Van Den Broek L.J.C.M., Fleuren G.J., Taminiau A.H.M. and Hogendoorn P.C.W. (1997). Distribution of extracellular matrix components in adamantinoma of long bones suggests fibrous-to-epithelial transformation. Hum. Pathol. 28, 183-188.

Hisaoka M., Morimitsu Y., Hashimoto H., Ishida T., Mukai H., Satoh H., Motoi T. and Mashinami R. (1999). Retroperitoneal liposarcoma with combined well-differentiated and myxoid malignant fibrous histiocytoma-like myxoid areas. Am. J. Surg. Pathol. 23, 1480-1492.

Hoffman M.A. and Dickersin G.R. (1983). Malignant fibrous histiocytoma. An ultrastructural study of eleven cases. Hum. Pathol. 14, 913-922.

Horvat B., Vrcic H. and Damjanov I. (1992). Transdifferentiation of murine squamous vaginal epithelium in proestrus is associated with changes in the expression of keratin polypeptides. Exp. Cell Res. 199, 234-239.

Iwasaki H., Isayama T., Ohjimi Y., Kikuchi M., Yoh S., Shinohara N., Yashitake K., Ishiguro M., Kamada N. and Enjoji M. (1992). Malignant fibrous histiocytoma. A tumor of facultative histiocytes showing mesenchymal differentiation in cultured cell lines. Cancer

69, 437-447.

Jawhari A.U., Farthing M.J.G. and Pignatelli M. (1999). The E-cadherin/epidermal growth factor receptor interaction. A hypothesis of reciprocal and reversible control of intercellular adhesion and cell proliferation. J. Pathol. 187, 155-157.

Katenkamp D. and Neupert G. (1982). Experimental tumors with features of malignant fibrous histiocytomas. Light microscopic and electron microscopic investigations on tumors produced by cell transplantation of an established fibrosarcoma cell line. Exp. Pathol. 22, 11-27.

Katz R.L., Quezado M., Senderowtcz A.M., Villalba L., Laskin W.B. and Tsokos M. (1997). An intra-abdominal small round cell neoplasm with features of primitive neuroectodermal and desmoplastic round cell tumor and a EWS/FLI1 fusion transcript. Hum. Pathol. 28, 502-509.

Kawai A., Woodruff J., Healey J.H., Brennan M.F., Antonescu C.R. and Ladanyi M. (1998). SYT-SSX gene fusion as a determinant of morphology and prognosis in synovial sarcoma. N. Engl. J. Med. 338, 153-160.

Kirkland S.C. (1988). Clonal origin of columnar, mucous, and endocrine cell lineages in human colorectal epithelium. Cancer 61, 1359-1363.

Knapp A.C. and Franke W.W. (1989). Spontaneous losses of control of cytokeratin gene expression in transformed, non-epithelial human cells occurring at different levels of regulation. Cell 59, 67-79.

Kounelis S., Jones M.W., Papadaki H., Bakker A., Swalsky P. and Finkelastein S.D. (1998). Carcinosarcomas (malignant mixed mullerian tumors) of the female genital tract: Comparative molecular analysis of epithelial and mesenchymal components. Hum. Pathol. 29, 82-87.

Krawisz S.R., Florine D.L. and Scott R.E. (1981). Differentiatioon of fibroblast-like cells into macrophages. Cancer Res. 41, 2891-2899.

Ladanyi M. (1995).The emerging molecular genetics of sarcoma translocations. Diagn. Mol. Pathol. 4, 162-173.

Lax S.F., Kendall B., Tashiro H., Slebos R.J.C. and Ellenson L.H. (2000). The frequency of p53, K-ras mutations, and microsatellite instability differs in uterine endometrioid and serous carcinoma. Evidence of distinct molecular genetic pathways. Cancer 88, 814-824.

Lawson C.W., Fisher C. and Gatter K.C. (1987). An immunohistochemical study of differentiation in malignant fibrous histiocytoma. Histopathology 11, 375-383.

Lengauer C., Kinzler K.W. and Volgelstein B. (1998). Genetic instabilities in humans. Nature 396, 643-649.

Mandahl N., Heim S., Arheden K., Rydholm A., Willen H. and Mitelman F. (1988). Rings, dicentrics, and telomeric association in histiocytomas. Cancer Genet. Cytogenet. 30, 23-33.

Mandahl N., Heim S., Willen H., Rydholm A., Eneroth M., Nilbert M., Kreicbergs A. and Mitelman F. (1989). Characteristic karyotypic anomalies identify subtypes of malignant fibrous hitiocytoma. Genes Chromosom. Cancer 1, 9-14.

Martel C., Harper F., Cereghini S., Noë V., Mareel M. and Crémisi C. (1997). Inactivation of retinoblastoma family proteins by SV40 T antigen results in creation of a hepatocyte growth factor/scatter factor autocrine loop associated with an epithelial-fibroblastoid conversion and invasiveness. Cell Growth Differ. 8, 165-178.

May W.A., Gishizky M.L., Lessnick S.L., Lunsford L.B., Lewis B.C., Delattre O., Zucman J., Thomas G. and Denny C.T. (1993a). Ewing's sarcoma 11;22 translocation produces a chimeric transcription factor that requires the DNA-binding domain encoded by FLI-1 for transformation. Proc. Natl. Acad. Sci. USA 90, 5752-5756.

May W.A., Lessnick S.L., Braun B.S., Klemsz M., Lewis B.C., Lunsford L.B., Hromas R. and Denny C.T. (1993b). The Ewing's sarcoma EWS/FLI-1 fusion gene encodes a more potent transcriptional activator and is a more powerful transforming gene than FLI-1. Mol. Cell Biol. 13,7393-7398.

McDowell E.M. and Trump B.F. (1981). Pulmonary small cell carcinoma showing tripartite differentiation in individual cells. Hum. Pathol. 12, 286.

Mckee P.H., Fletcher C.O.M., Stavrinos P. and Pambakian H. (1990). Carcinosarcoma arising in eccrine spiradenoma (a clinicopathologic and immunohistochemical study of 2 cases). Am. J. Dermatopathol. 12, 335-343.

McManus A.P., Gusterson B.A., Pinkerton C.R. and Shipley J.M. (1996). The molecular pathology of small round-cell tumors - relevance to diagnosis, prognosis, and classification. J. Pathol. 178, 116-121.

Meis J.M. (1991). "Differentiation" in bone and soft-tissue tumors. A histological indicator of tumor progression. Pathol. Ann. 26, 37-62.

Miettnen P.J., Ebner R., Lopez A.R. and Derynck R. (1994). TGF-beta induced transdifferentiation of mammary epithelial cells to mesenchymal cells: Involvement of type I receptors. J. Cell Biol. 127, 2021-2036.

Molenaar W.M. and Muntinghe F.L.H. (1999). Expression of neural cell adhesion molecules and neurofilament protein isoforms in Ewing's sarcoma of bone and soft tissue sarcomas other than rhabdomyosarcoma. Hum. Pathol. 30, 1207-1212.

Nakajima M., Kasai T., Hashimoto H. and Manabe I.Y. (1999). Sarcomatoid carcinoma of the lung. A clinicopathologic study of 37 cases. Cancer 86, 608-616.

Ng H.K. and Poon W.S. (1990). Gliosarcoma of the posterior fosa with features of a malignant fibrous histiocytoma. Cancer 65, 1161-1166

Nobukawa B., Fujii H., Hirai S., Kumasaka T., Shimizu H., Matsumoto T., Suda K. and Futagawa S. (1999). Breast carcinoma diverging to aberrant melanocytic differentiation. A case report with histopathologic and loss of heterozygosity analyses. Am. J. Surg. Pathol. 23, 1280-1287.

Noguera R., Navarro S., Cremades A., Roselló-Sastre E., Pellín A., Peydro-Olaya A. and Llombart-Bosch A. (1998). Translocation X18 in a biphasic synovial sarcoma with morphologic feature of neural differentiation. Diagn. Mol. Pathol. 7, 16-23.

Ordónez N.G. (1998). Desmoplastic small round cell tumor II. An ultrastructural and immunohistochemical study with emphasis on new immunohistochemical markers. Am. J. Surg. Pathol. 22, 1314-1327.

Orndal C., Mandahl N., Rydholm A., Willen H., Brosjo O., Heim S. and Mitelman F. (1992). Supernumerary ring chromosomes in five bone and soft tissue tumors of low or borderline malignancy. Cancer Genet. Cytogenet. 60, 170-175.

Orndal C., Rydholm A., Willen H., Mitelman F. and Mandahl N. (1994). Cytogenetic intratumor heterogeneity in soft tissue tumors. Cancer Genet. Cytogenet. 78, 127-137.

Osanai T., Yamakawa M., Suda A. and Watanabe Y. (2000). Metamorphosed fibroblasts and their relation to the histogenesis of malignant fibrous histiocytoma in experimental murine model. Histol. Histopathol. 15, 697-705.

Otis C., Kreb P.A., Quezado M.M., Albuquerque A., Bryant B., San Juan X., Kleiner D., Sobel M.F. and Merino M.J. (2000). Loss of heterozygosity in p53, BRCA1, and estrogen receptor genes and

correlation to expression of p53 protein in ovarian epithelial tumors of different cell types and biological behavior. Hum. Pathol. 31, 233-238.

Padmore R.F., Lara J.F., Ackerman D.J., Gales T., Sigurdson E.R., Ehya H., Cooper H.S. and Patchefsky A.S. (1996). Primary combined malignant melanoma and ductal carcinoma of the breast. A report of two cases. Cancer 78, 2515-2525.

Pagan R., Martin I., Alonso A., Llobera M. and Vilaro S. (1996). Vimentin filaments follow the pre-existing cytokeratin network during epithelial mesenchymal transition of cultered neonatal rat hepatocytes. Exp. Cell Res. 222, 333-334.

Piek E., Moustakas A., Kurisaki A., Heldin C.H. and tenDijke P. (1999) TFG-(beta) type I receptor/ALK-5 and Smad ptoteins mediate epithelial to mesenchymal transdifferentiation in NmuMG breast epithelial cells. J. Cell Sci. 112 (Pt24), 4557-4568.

Pierotti M.A., Bongarzone I., Borrello M.G., Greco A., Pilotti S. and Sozzi (1996). Cytogenetics and molecular genetics of carcinomas arising from thyroid epithelial follicular cells. Genes Chromosom. Cancer 16,1-14

Pilotti S., Torre G.D., Lavarino C. Palma S.D., Sozzi G., Minoletti F., Rao S., Pasquini G., Azzarelli A., Rilke F. and Pierotti M. A. (1997). Distinct mdm2/p53 expression patterns in liposarcoma subgroups implications for different pathogenetic mechanisms. J. Pathol. 181, 14-24.

Pitt M.A., Swells S. and Eyden B.P. (1995). Carcinosarcoma arising in a duct papilloma. Histopathology 26, 81-84.

Przygodzki R.M., Koss M.N., Moran C.A., Langer J.C., Swalsky P.A., Fishback N., Bakker and Finkelstein S.D. (1996). Pleomorphic (giant and spindle cell) carcinoma by K-ras-2 and p53 analysis. Am. J. Clin. Pathol. 106, 487-492.

Ro J.Y., Ayala A.G., Sella A., Samuels M.L. and Swanson D.A. (1987). Sarcomatoid renal cell carcinoma: A clinicopathologic study of 42 cases. Cancer 59, 516-526.

Ro J.Y., Chen J.L., Lee J.S. Salim A.A., Ordónez N.G. and Ayala A.G. (1992). Sarcomatoid carcinoma of the lung: Immunohistochemical and ultrastructural studies of 14 cases. Cancer 69, 376-386.

Roholl P.J.M., Kleijne J. van Basten C.D.H., van der Putte S.C.J. and van Unnik J.A.M. (1985a). A study to analyze the origin of tumor cells in malignant fibrous histiocytomas. A multiparametric characterization. Cancer 56, 2809-2815.

Roholl P.J.M., Kleyne J. and van Unnik J.A.M. (1985b). Characterization of tumor cells in malignant fibrous histiocytomas and other soft tissue tumors, in comparison with malignant histiocytes. II. Immunoperoxidase study on cryostat sections. Am. J. Pathol. 121, 269-274.

Rosai J., Akerman M., Cin P.D., Dewever I., Fletcher C.D.M., Mandahl N., Mertens F., Mitelman F., Rydholm A., Sciot R., Tallini G., Van Den Berghe H., Van De Ven W., Vanni R. and Willwn H. (1996). Combined morphologic and karyotypic study of 59 atypical lipomatous tumors. Evaluation of their relationship and differential diagnosis with other adipose tissue tumors. (A report of the CHAMP study group). Am. J. Surg. Pathol. 20, 1182-1189.

Sakamoto K. (1986). Malignant fibrous histiocytoma induced by intra-articular injection of 9,10-dimethyl-1, 2-benzanthracene in the rat. Pathological and enzyme histochemical studies. Cancer 57, 2313-2322.

Sato H., Hasegawa I., Abe Y., Sakai H. and Hirohashi S. (1999). Expression of E-cadherin in bone and soft tissue sarcomas: A possible role in epithelial differentiation. Hum. Pathol. 30, 1344-1349.

Schneider P., Busch U., Meister H., Qasem Q. and Wunsch P.H. (1999). Malignant fibrous histiocytoma (MFH). A comparison of MFH in man and animals. A critical review. Histol. Histopathol. 14, 845-860.

Semat A., Duprey P., Vasseur M. and Darmon M. (1986). Mesenchymal-epithelial conversions induced by 5-azacytidine: appearance of cytokeratin endo-A messenger RNA. Differentiation 31, 61-66.

Shannon R.L., Ro J.Y., Grignon D.J., Ordónez N.G., Johnson D.E., Mackay B., Tetu B. and Ayala A.G. (1992). Sarcomatoid carcinoma of the prostate. A clinicopathologic study of 12 patients. Cancer 69, 2676-2682.

Shirasuna K., Sugiyama M. and Miyazaki T. (1985). Establishment and characterization of neoplastic cells from a malignant fibrous histiocytoma. A possible stem cell line. Cancer 55, 2521-2532.

Snover D.C., Sumner H.W. and Dehner L.P. (1982). Variability of histologic pattern in recurrent soft tissue sarcomas originally diagnosed as liposarcoma. Cancer 49, 1005-1015.

Sonobe H., Takeuchi T., Taguchi T., Shimizu K., Iwata J., Furihata M. and Ohtsuki Y. (1999). Further characterization of the human clear cell sarcoma line HS-MM demonstrating a specific T(12;22) (q13;q12) translocation and hybrid EWS/ATF-1 transcript. J. Pathol. 187, 594-597.

Sorensen P.H.B., Shimada H., Liu X.F., Lim J.F., Thomas G. and Triche T.J. (1995). Biphenotypic sarcomas with myogenic and neural differentiation express the Ewing's sarcoma EWS/FLI-1 fusion gene. Cancer Res. 55, 1385-1392

Sreenan J.J. and Hartn W.R. (1995). Carcinosarcomas of the female genital tract. A pathologic study of 29 metastatic tumors: Further evidence for the dominant role of the epithelial component and the conversion theory of histogenesis. Am. J. Surg. Pathol. 19, 666-670.

Strauchen J.A. and Dimitriu-Bona A.D. (1986). Malignant fibrous histiocytoma. Expression of monocyte/macrophage differentiation antigens detected with monoclonal antibodies. Am. J. Pathol. 124, 303-309.

Teitell M.A., Thompson A.D., Sorensen P.H.B., Shimada H., Triche J.J. and Denny C.T. (1999). EWS/ETS fusion genes induce epithelial and neuroectodermal differentiation in NIH 3T3 fibroblasts. Lab. Invest. 79, 1535-1543.

Thompson L., Chang B. and Barsky S.H. (1996). Monoclonal origins of malignant mixed tumors (carcinosarcomas). Evidence for a divergent histogenesis. Am. J. Surg. Pathol. 20, 277-285.

Thorner P., Squire J., Chilton-MacNeill S., Marrano P., Bayani J., Malkin D., Greenberg M., Lorenzana A. and Zielensba M. (1996). Is the EWS/FLI-I fusion transcript specific for Ewing's sarcoma and peripheral primitive neuroectodermal tumor? A report of four cases showing this transcript in a wider range of tumor types. Am. J. Pathol. 148, 1125-1138.

Tsao M.S. and Grisham J.W. (1987). Hepatocarcinomas, cholangiocarcinomas, and hepatoblastomas produced by chemically transformed cultured rat liver epithelial cells. Am. J. Pathol. 127, 169-181.

Tsarfary I., Rong S., Ressau J.H., Rulong S., da sliva P.P. and Vande Woude G.F. (1994). The Met proto-oncogene mesenchymal to epithelial cell conversion. Science 263, 98-101.

Vallés A.M., Boyer B., Tucker G.C., Badet J., Barritault D. and Thiery J.P. (1990). Acidic fibroblast growth factor is a modulator of epithelial plasticity in a rat bladder carcinoma cell line. Proc. Natl. Acad. Sci.

USA 87, 1124-1128.

von Koskull H. and Virtanen I. (1987). Induction of cytokeratin expression in human mesenchymal cells. J. Cell Physiol. 133, 321-329.

Wada H., Enomoto T., Fujita M., Yosino K., Nakashima R., Kurachi H., Haba T., Wakasa K., Shroyer K.R., Tsujimoto M., Hongyo T., Komura T. and Murata Y. (1997). Molecular evidence that most but not all carcinosarcomas of the uterus are combination tumors. Cancer Res. 57, 5379-5385.

Wang D.R. (1990). Cell transdetermination. In: Cytobiology. 1st edn. Wang K.R., Xue S.B. and Liu H.T. (eds). Beijing Normal University Publishing House. pp 460-465.

Ward J.M., Stevens J.L., Konishi N., Kurata Y., Uno H., Diwan B.A. and Ohmori T. (1992). Vimentin metaplasia in renal cortical tubules of preneoplastic, neoplastic, aging and regenerative lesions of rats and humans. Am. J. Pathol. 141, 955-964.

Wargotz E.S. and Norris H.J. (1989). Metaplastic carcinoma of the breast III Carcinosarcoma. Cancer 64, 1490-1499.

Wu M-S., Chang M-C., Huang S-P., Tseng C-C., Sheu J-C., Lin Y-W., Shun C-T., Lin M-T. and Lin J-T. (2001). Correlation of histologic subtypes and replication error phenotype with comparative genomic hybridization in gastric cancer. Genes Chromosom. Cancer 30, 80-86.

Yokoyama R., Mukai K., Hirota T., Beppu Y. and Fukuma H. (1996). Primary malignant melanoma (clear cell sarcoma) of bone: report of a case arising in the Ulna. Cancer 77, 2471-2475.

Yumoto T. and Morimoto K. (1980) Experimental approach to fibrous histiocytoma. Acta Pathol. Jpn. 30, 767-778.

Zhang Z. and Xie F.P. (1994). Transdifferentiation of neoplastic cell. Foreign Medical Science (Oncology) 21 suppl., 8-9 (in Chinese).

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