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Review Article

Diplomatic Epic of P63-An Immunohistochemical Marker and its Role in Perplex Neoplasms - A Review

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ABSTRACT

P63 is basically a stem cell marker. It belongs to p53 protein family which comprises of transcription factors p53, p63, p73. P63 also possesses two isoforms which are interestingly with opposing characters. Its complexity remains unrevealed with helps in maintenance of genetic stability of germ cells, mechanisms of p63 behaves both monogenic as well as tumor suppressor of its various isoforms.

P53 family regulates many vital biological process including cell differentiation, proliferation and cell death / apoptosis. Phylogenetic analysis revealed that p53 family was originated from p63 / p73-like ancestral gene early in metazoan evolution.P63 shows expression in various neoplasms, it is typically used as stem cell marker. Various evidences show over expression of p63 in squamous cell carcinoma.

Unlike other exocrine glands salivary gland possess typical myoepithelial cells that have the ability to transform as neoplastic cell. Tumors of salivary glands are quiet interesting, based on studies done in population of atomic- bomb survivors in Hiroshima and Nagasaki, radiation seems to provoke salivary gland neoplasms.

In this review we are going to overlook anthropogenesis of p63 and its role in various neoplasms.

Key words: P63, Immunohistochemical Marker, Perplex neoplasm.

REVIEW OF P63 AND SALIVARY GLAND NEOPLASMS

In comparison with the exocrine pancreas, an astonishing variety of tumors occurs in the salivary glands. Many tumors which are quite common in the salivary glands never occur in the pancreas. On the other hand, many types of tumors in the salivary glands also can be observed in the mammary gland. The main reason for this peculiarity is that in the salivary glands, as well as in the breast, myoepithelial cells are an important component.

MYOEPITHELIAL CELLS

In recent years, the investigation of salivary gland tumors, with the aid of the electron microscope, has considerably enlarged our knowledge about the role of these cells; in the following discussion, special emphasis will be given to the fine structural organization of salivary gland tumors containing myoepithelial cells. In the parotid gland, myoepithelial cells were first described by Zimmermann in 1898.

As the name indicates, these cells lie at the base of the epithelial layer of the acini or at the base of the intercalated or striated

ducts. They exhibit a stellate cell body, and therefore they have also been named basket cells. It is assumed that in spite of their intra-epithelial position these cells act as smooth muscle cells and facilitate the secretion into the secretory ducts. [1]

EVOLUTION OF THE p53 FAMILY MEMBERS

Tau antigens (also known as cellular or non viral tumor antigens) were detected in uninfected and simian virus 40-infected monkey cells after immuno precipitation with serum from hamsters bearing simian virus 40-induced tumors (anti-T serum). These two proteins (56,000 daltons) were digested to similarly sized peptides with various amounts of Staphylococcus aureus V8 protease. The Tau antigen isolated from infected monkey cells was closely related but was not identical to the corresponding protein from human cells transformed by simian virus 40, as determined by two-dimensional mapping of their methionine-labeled trypticpeptides. Hamster cells transformed by various primate papova viruses (simian virus 40, BK virus, and JC virus) synthesized indistinguishable Tau antigens, as determined by two-dimensional peptide mapping. When tested by the same procedure, these proteins and the ones made in monkey and human cells were found to be related to the Tau antigens isolated from simian virus 40-transformed mouse and rat cells. Based on these results, an "evolutionary tree" was constructed to show the relationship among the methionine-containing tryptic peptides of all of these proteins. [2]

STRUCTURE, FUNCTION AND REGULATION OF P63

The p53 tumor suppressor gene is one of the most frequently mutated genes in human cancers. p53 is a sequence-specific transcription factor and plays a critical role in activating the expression of genes involved in cell cycle arrest or apoptosis under conditions of genotoxic stress. For over two decades, p53 was thought to be the only gene of its kind in the vertebrate genomes. This strong conviction, which was widely accepted in the p53 field, has now been proven to be incorrect. Two genes, referred to as p63 and p73, have been found to encode proteins that share a significant amino-acid identity in the transactivation domain, the DNA binding domain, and the oligomerization domain with p53. [3]

p63is a recently cloned homologue of the p53 tumor suppressor gene. In contrast to p53, the p63 gene encodes for at least six major isotypes. Three isotypes (TAp63α, TAp63β, and TAp63γ) contain the transactivating (TA) domain and are able to transactivatep53 reporter genes and induce apoptosis. In contrast, the other three isotypes (DNp63α, DNp63β, and DNp63γ) are transcribed from an internal promoter localized within intron 3, lack the TA domain, and act as dominant-negatives to suppress transactivation by both p53 and TAp63 isotypesp63 is a recently cloned homologue of the p53 tumor suppressor gene. In contrast to p53, the p63 gene encodes for at least six major isotypes. [4] Three isotypes (TAp63α, TAp63β, and TAp63γ) contain the transactivating (TA) domain and are able to transactivatep53 reporter genes and induce apoptosis. In contrast, the other three isotypes (ΔNp63α, ΔNp63β, and ΔNp63γ) are transcribed from an internal promoter localized within intron 3, lack the TA domain, and act as dominant-negatives to suppress transactivation by both p53 and TAp63 isotypes.

p63 is expressed as three major forms, p63 α, p63 β and p63 γ, each of which differ in theirC-termini. All three forms can be alternatively transcribed from a cryptic promoter located within intron 3, producing ΔNp63α, ΔNp63β and ΔNp63 γ. [5]

P63, STEM CELL MARKER IN IN SITU AND INVASIVE CUTANEOUS EPITHELIAL LESIONS

P63, a nuclear transcription factor that triggers keratinocyte differentiation, is down-regulated in terminally differentiated cells. [6]

P63 IN SQUAMOUS CELL CARCINOMA

In squamous cell carcinomas of the skin, a significant increase in p63 expression, both in terms of intensity and distribution, is seen relative to normal skin, as the proliferative fraction is expanded in tumors. Examination of skin lesions ranging from kerato acanthoma to a grade IV spindle cell carcinoma revealed very strong p63 immunoreactivity in grade 3 SCC with decrease in a single grade IV spindle SCC. In these tumors, carcinoma *in situ* was characterized by p63 immunoreactivity in all layers. While ΔNp63α was shown to be the most over expressed isoformin squamous cell tumors, careful characterization of the TA and ΔN isoforms from different tissue and tumor types revealed that individual isoforms are differentially expressed in the neoplastic transformation of different tissue types, implying specific contributions of the isoform expressed in a context-dependent manner. While ΔNp63α is over expressed in primary skin tumors, expression of TAp63 is not a common event but has been reported to be down regulated relative to normal skin using PCR-based methods. [7]

P63 IN TUMORIGENESIS

p63 participates in the cellular signalling processes following DNA damage by controlling cell cycle arrest and apoptosis and therefore it is also important in cancer development. Probably, it does not function as a basic tumour suppressor because it is rarely mutated in human cancers. In most cases, tumours maintain p63 expression and moreover the *TP63* locus is sometimes amplified and thus p63 is over expressed. [8]

P63 EXPRESSION IN CANCER

Mutations of p63 are extremely rare in human cancers, indicating it is not a canonical tumor suppressor. Most tumors (>80% of primary head and neck squamous cell carcinomas (HNSCCs), as well as other squamous cell epithelial malignancies and non-small cell lung cancer) retain p63 expression, where it is often over expressed and occasionally amplified Frequently, tumors have simultaneous transcriptional upregulation of both TAp63 and DNp63 isoforms, with DNp63 being predominant at the protein level. [9]

P63 IS A SUPPRESSOR OF METASTASIS

More aggressive, metastatic tumors lose p63 expression, suggesting that p63 loss accelerates tumorigenesis and metastatic spread. [10] Correspondingly, disruption of p63 in squamous cell lines results in upregulation of genes associated with increased invasiveness and metastasis in tumors. [11] This suggests that p63 is a marker of non-invasive epithelial tumors [12] such as ductal carcinoma in situ of the breast or prostatic intraepithelial neoplasia. Indeed, sclerosingadenosis or small foci of dense fibrosis with distortion of the normal acinar architecture, remain p63 positive. This highlights the potential value of p63 as a differential diagnostic marker of tumors with more benign properties. [9]

EXPRESSION OF P63 IN SQUAMOUS AND TRANSITIONAL CARCINOMAS

We found a good correlation between the staining patterns seen in normal tissues and the immunoreactivity encountered in corresponding neoplastic samples. In general, tumors derived from stratified epithelia showed strong p63 nuclear reactivities. Similarly, transitional cell carcinomas of the bladder displayed p63 positivity. Additionally, we observed p63 nuclear reactivity within regions of squamous cell differentiation in other tumors, such as ovarian endometrioid tumors and teratomas of both testes and ovaries. All adenocarcinomas analyzed, including those derived from breast and prostate, as well as mesotheliomas and hepatocellular carcinomas, and had undetectable p63 levels. [13]

P63 AS A DIAGNOSTIC TOOL FOR POORLY DIFFERENTIATED AND UNDIFFERENTIATED CARCINOMAS

Metastatic carcinomas of unknown primary site represent about 2% to 5% of all newly diagnosed carcinomas. Light

microscopic examination reveals that about 30% of carcinomas of unknown primary site are poorly differentiated or undifferentiated carcinomas. Within this heterogeneous tumor group, only extragonadal germ cell tumors and neuroendocrine carcinomas are treated by chemotherapy, irrespective of their primary site. In contrast, knowing the primary site of somatic non neuroendocrine carcinomas of unknown primary site would be of clinical importance, as patients then could be treated according to protocols that are specific for advanced stages of the respective carcinoma types. Furthermore, lacking knowledge of the primary tumor site poses an additional psychological burden on patients and their families. The immunohistochemical identification of primary carcinoma sites usually is based on the detection of more or less organ-specific terminal differentiation products or transcription factors. Most of these markers are commercially available and substantially facilitate the identification of primary sites of metastatic adenocarcinomas, but often have a low sensitivity in poorly differentiated carcinomas. Therefore, instead of using organ-specific markers, in poorly differentiated carcinomas it might be more rewarding to use markers that are associated with minimal ”histogenetic” differentiation. For instance, the expression of markers specifically associated with squamous differentiation limits the possible primary site of a carcinoma for practical purposes to only a few locations (head/neck, lungs, esophagus, and cervix uteri). [14]

Since the mid-1980s, commercially available monoclonal antibodies recognizing basal cell–type high-molecular weight cytokeratins (CKs) 5 and 14 according to the catalog by Moll et al were established as the most sensitive, although not entirely specific, paraffin-reactive markers associated with a squamous differentiation in carcinomas. The recently cloned transcription factor p63 is another promising marker to indicate a minimal squamous differentiation in a poorly differentiated carcinoma. [15]

P63 IS EXPRESSED IN A SUBSET OF B-CELL LYMPHOMAS.

We examined a number of non-Hodgkin’s B-cell lymphomas, including those classified as chronic lymphocytic leukemia/ small lymphocytic lymphoma, FL, DLCL, anaplastic large-cell lymphoma, mantle cell lymphoma, and marginal zone lymphoma. Specifically, we observed diffuse to intense staining in DLCL and FL (grade 2 and 3). Furthermore, in FL, the strongest staining was observed in grade 3 cases in the larger neoplastic cells. In chronic lymphocytic leukemia, the three positive cases showed focal, weak p63 reactivity in what appeared to be infiltrating normal lymphocytes rather than the neoplastic component (data not shown). We found no association between p53 and p63 immunoreactivity (data not shown). To determine which p63 isoforms were present in lymphoid tissues, we performed RT-PCR using isoform-specific primers on total RNA from normal lymph node and six lymphomas. With the exception of the ΔNp63 isoforms, all other TAp63 products were expressed in the normal lymph node. The subset of six lymphomas analyzed, including three DLCLs and three FLs, showed a similar pattern of p63 expression. Interestingly, we were able to detect the Δ Np63 isoform(s) in two of the three FL cases, but not in the DLCL samples. [13]

P63 EXPRESSION IN NORMAL SALIVARY GLAND

p63-reactive nuclei were seen in basal cells around luminal cells in intercalated, striated, and some interlobular ducts. Small, often elongated nuclei at the periphery of the acini were also p63-reactive. The location of these p63-reactive nuclei suggested that the p63-reactive cells in the acini were myoepithelial cells. Luminal duct cells and acinar cells were unreactive. [16] p63 is expressed in the nuclei of normal human salivary gland myoepithelial and basal duct cells as well as retained in the modified myoepithelial and basal cells of human salivary gland tumors which suggests a role for p63 in

oncogenesis of these complex tumors. A better characterization of salivary gland myoepithelial cells may provide valuable information regarding maintenance of this tissue, histogenesis and oncogenesis of salivary gland tumors, and may have clinical utility for the diagnosis. [16]

P63 EXPRESSION IN THE SALIVARY GLAND NEOPLASMS ADENOID CYSTIC CARCINOMA

The participation of myoepithelial cells in certain salivary gland neoplasms such as adenoid cystic carcinoma is generally accepted. Our results are in agreement with this view. We found strong positive p63 nuclear staining in 12 of 15 ACCs examined. The 2 cases of ACC with no immunoreactivity and the 1 case with weak p63 immunoreactivity were predominantly of the solid variant. Nevertheless, most solid ACCs examined showed strong p63 immunoreactivity. [17]

POLYMORPHOUS LOW-GRADE ADENOCARCINOMA

Polymorphous low-grade adenocarcinoma appears to show little evidence of myoepithelial differentiation, although this view has been challenged. [17]

BASAL CELL ADENOMAS

Variable p63 staining was identified in basal cell adenoma. All parotid gland basal cell adenomas stained strongly for p63, with localization to the peripheral tumor cells situated adjacent to the connective tissue stroma. [17]

CANALICULAR ADENOMAS

All basal cell adenoma variant exhibits some degree of myoepithelial cell participation while peri ductal, epithelioid and spindled (stromal-like) morphologic structures. Only the canalicular adenomas even if mixed with solid and trabecular patterns are devoid of the antibody suggesting an adenoma composed exclusively of ductal luminal cells. [18]

P63 IN DENTIGEROUS CYST AND AMELOBLASTOMA

Odontogenic cysts and tumors constitute an important aspect of oral and maxillofacial pathology. Although they arise from the same odontogenic apparatus, they are distinct entities with different pathogenesis and differ considerably in their biological behaviour in terms of aggression and capacity to spread (metastasis). This could be attributed to the nature of their epithelium and alteration in the cell cycle control. P63 plays an essential role in epithelial development and the proliferation of limb and craniofacial structure. P63 stains the nuclei of basal or progenitor cells in a variety of epithelia. In recent studies up regulated expression and/or activity of p63 have been demonstrated in malignancies. In the present study, the expression of p63 in DC is mild inbasal layer, and ameloblastoma showed intense staining in the peripheral columnar/ cuboidal cells and central stellate cells. The expression of p63 suggests that these p53 homologs play a role in differentiation and proliferation of odontogenic epithelial cells. Variations of predominantly expressed isoform suggest that p63 might differentially function in odontogenic tissues. [19]

P63 IN LUNG CANCER

The importance of p63 in lung cancer development is also outlined by the finding that p63 expression increases from hyperplasia to metaplasia, to dysplasia reaching its maximum in severe grade dysplasias. [20]

USEFUL PANEL OF MARKER IN DISTINGUISHING SMALL CELL CARCINOMA OF LUNG FROM SQUAMOUS CELL CARCINOMA OF LUNG

The histopathologic distinction of small cell from non–small cell carcinoma of lung is important therapeutically. However, such distinction may not always be straight forward based on morphologic findings alone, especially in cytologic specimens, but in tissue specimens as well. In particular, distinguishing the intermediate type of small cell lung carcinoma (SCLC) from poorly differentiated squamous cell carcinoma (PDSCC) can be difficult even in experienced hands.

In a histochemical study of lung neoplasms, p63, a p53-related nuclear protein was expressed consistently in PDSCC and not in SCLC. [21]

P63 A HELPFUL TOOL IN POORLY DIFFERENTIATED AND UNDIFFERENTIATED RENAL MALIGNANCIES, TO DISTINGUISH FROM TRANSITIONAL-CELL CARCINOMA AND RENAL CELL-CARCINOMA

Differential diagnosis of renal-cell carcinomas (RCCs) and transitional-cell carcinomas (TCCs) of the renal pelvis can be difficult, especially if tumors are poorly differentiated or undifferentiated. However, a correct diagnosis is essential with respect to surgical treatment and follow-up because of the well known risk for tumor recurrence in the ureter and/or bladder in patients with pelvic TCC.

On the other hand, strong expression of p63 was detected both in normal pelvic urothelium and TCCs. The staining pattern of p63 in normal pelvic urothelium is identical to that of bladder mucosa This indicates that, with respect to p63, upper tract TCCs are comparable to bladder cancer. Recently, a decrease of TAp63 and an increase of DeltaNp63 in bladder TCCs compared to normal urothelium were detected by quantitative PCR analysis. Regarding patient survival, the altered TAp63 expression reached borderline significance. Therefore, we are now investigating whether p63 immunoreactivity is related to prognosis in patients with TCC. [22]

EXPRESSION OF P63 IN NORMAL AND NEOPLASTIC BREAST TISSUE

In normal breast tissue, self-renewing stem cells divide and produce 1 daughter cell, which maintains the features of a stem cell. The other cell develops into the primary progenitor cell. The primary progenitor cell is committed to producing both ductal and alveolar progenitor cells. The progeny of both ductal and alveolar progenitor cells are luminal epithelial cells and myoepithelial cells. Expression of p63 was infrequent in breast carcinomas (11.76% of cases), arguing against a direct role in mammary tumorigenesis. However, among the 10 cases positive for p63 only 1 case expressed p53. These findings are surprising because p63 is expressed only in poorly differentiated ductal carcinomas in which expression of p53 was frequent. These data suggest that, like p73, p63 may act indirectly as an oncogene by inhibiting p53. This hypothesis also could explain why p63 correlated with several indicators of poor prognosis and warrants further investigation. [23]

In all cases, p63 expression was nuclear. In normal breast tissue present in the examined sections, consistent, intense staining of nuclei of normal myoepithelial cells of breast lobules and ducts was noted. These cells also exhibited cytoplasmic immunoreactivity for S-100 protein and α-smooth actin, and membranous immunoreactivity for Ck14. Although all cells with location and morphology of myoepithelial cells stained with anti-p63, occasionally (less than 1%) they did not stain for the other markers. [24]

P63 IMMUNOREACTIVITY IN BENIGN BREAST LESIONS

In all benign lesions, p63 immunoreactivity was noted in the myoepithelial cell layer surrounding the epithelial structures. Staining intensity was comparable to that of normal breast tissue. Scattered, weakly p63-positive epithelial cells (<5%) were found in almost half of the ductal hyperplasia cases (22/48, 45%). Similar luminal epithelial staining was noted with Ck14. A higher percentage of luminal epithelial cells (approximately 10-15%) stained positive with S-100.

Interestingly, in all cases with papillomatosis there was strong p63 and S100 immunostaining in 5-10% and in 20-30% of luminal epithelial cells respectively. Weak staining was noted in <5% of epithelial cells with the antibody Ck14, while no epithelial staining was observed with anti-a-smooth actin. [24]

P63 IMMUNOREACTIVITY IN CARCINOMA IN-SITU BREAST LESIONS

A peripheral rim of myoepithelial cells was also highlighted with p63-staining in all in situ carcinomas. Although the staining intensity was similar to that of non-neoplastic tissues, there was a less continuous peripheral rim of cells, as compared with normal structures. The p63-negative basally located cells were negative for the other myoepithelial cell markers as well. [24]

P63 IMMUNOREACTIVITY IN MALIGNANT BREAST LESIONS

Regarding epithelial cells, strong nuclear p63 immunoreactivity was noted in a minor fraction of neoplastic cells (10-15%) in 62.5% (15/24) of in situ ductal carcinomas papillary-type. Comparable staining was observed with S-100. All neoplastic cells in ductal carcinomas in situ, of non-papillary type, were negative for p63 and α-smooth muscle actin, while a small fraction (less than 5%) was positive for S-100 and CK14.

All invasive breast carcinomas were devoid of p63 staining. A small fraction of p63-positive neoplastic cells (10-15%) was noted in 33.3% (9/27) of invasive papillary carcinomas. Comparable staining was observed with S-100. Positive neoplastic cell staining was found in 20% of invasive ductal carcinomas, NST, with S-100 (strong, cytoplasmic) and cytokeratin 14 (weak, membranous). The positive immunostaining was confined to the stromal-epithelial junction of the infiltrating tumor cells. [24]

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