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Original Article

CD44 and p53 immunoexpression patterns in NF1 neoplasms - indicators of malignancy and infiltration

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Abstract: Neurofibromatosis type 1 (NF1) provides a unique system to evaluate the complete range of neoplastic expressions, from encapsulated benignity to invasiveness and malignancy. This study was aimed at determining whether CD44 and p53 may serve as indicators of malignant progression of neurofibroma. CD44, a transmembrane glycoprotein receptor for hyaluronic acid, and participates in cell-extracellular matrix interactions and migration. CD44 may play a vital role, either through under or overexpression, with invasion and metastases of tumors, altering their ability to infiltrate the adjacent tissue. The tumor suppressor gene, p53, has also been implicated in malignant progression of various human tumors including malignant peripheral nerve sheath tumors (MPNST). A total of 44 tumors from 33 patients with NF1 were evaluated with an anti-human CD44H, CD44 splice variant v6 and anti-p53 monoclonal antibodies. Morphologic expression patterns of expression were evaluated for CD44 while semiquantitative criteria were applied to assess, p53 nuclear positivity. Immunoexpression of p53 was markedly higher in 12 of 16 MPNST (75%). Thirteen of 28 (46%) benign neurofibroma also had some expression of p53 above 'normal level', although much lower than the MPNST. Plexiform neurofibroma did not differ from other benign lesions in their expression of p53. Our results suggest that p53 mutation as evidenced by immunohistochemical overexpression is a factor in malignant transformation and progression of neurofibroma. 70% of benign neurofibroma demonstrated some, usually focal, CD44 positivity. The pattern of CD44 expression in plexiform neurofibroma was revealing, as it was maximal in the 'nonencapsulated' portions of the tumors. Eight of 11 (72%) locally infiltrative cutaneous neurofibroma and 13 of 16 (81%) MPNST exhibited diffuse CD44 positivity. CD44v6 expression was positive in control tissues but was not identified in any of tumor samples. Also, within the confines of encapsulated tumors CD44 expression is limited, while in poorly circumscribed neurofibroma CD44 expression is upregulated. This is interpreted as a reflection of the interaction of CD44+ tumor cells with extracellular matrix, hence facilitating infiltrative behavior.

Keywords: Neurofibromatosis type 1 (NF1), CD44, p53, tumor markers, infiltration, immunohistochemistry

Introduction

Neurofibroma are common benign peripheral nerve sheath tumors that occur sporadically as solitary nodules, or as multiple lesions in patients with NF1. Neurofibroma most commonly occur as cutaneous nodules, however, they may be found along any peripheral nerve, plexus or trunk. Malignant transformation occurs in approximately 5% of large plexiform lesions, but is rare in cutaneous and soft tissue neurofibroma. Malignant transformation is also more likely in patients with NF1 [1]. Malignant peripheral nerve sheath tumors (MPNST) are uncommon, aggressive malignancies that arise within peripheral nerves and account for approximately 5% of soft tissue tumors. They may arise spontaneously; however, around 60% arise from neurofibroma, often of the plexiform type. Although rare in the general clinical population (incidence of 0.001%), MPNST arise in 8-13% of patients with neurofibromatosis 1[2-4]. These tumors can be highly metastatic and often recur after resection and radiation therapy, often leading to death within 10 years of diagnosis. Due to this fact, MPNST are a major factor con-

tributing to NF1 patient mortality [5, 6].

The putative tumor suppressor gene, p53, has been shown to play an important role in many malignancies [7, 8]. The p53 gene is located on the short arm of chromosome 17 and contains 393 amino acids. The wild type p53 represses abnormal cell proliferation and growth by acting at various cellular pathways. In recent years there has been additional evidence to suggest that genetic alterations at sites other than the NF1 gene may be important in the malignant transformation of NF1 neoplasms [9-13]. A possible candidate in this process is p53, which has clearly been shown to play a role in various other cancers [14-16].

CD44 is a major cell surface receptor for hyaluronic acid that is included in the group of cell adhesion molecules and is a membrane glycoprotein that is found in a wide variety of cell types. In lymphocytes, it functions as a homing receptor, but more importantly it is recognized for its interactions with various extracellular matrix components including hyaluronic acid. CD44 has multiple isoforms that are generated by alternative splicing of the mRNA, including or excluding certain exons. These variant exons (v3-v10) contribute to the molecule's ability to mediate significantly different functions, playing roles in cell-cell and cell-matrix adhesion and activation of high-affinity growth factor receptors. The extracellular matrix interactions of CD44 and its isoforms have also been shown to play a role in the growth of and infiltrative and metastatic behavior of various tumors [17-20]. The standard form of CD44 is present on the surface of most human cells. Altered levels of CD44 expression have been detected in many types of human neoplasms [21-23]. Thus detection of abnormal regulation of CD44 splicing could be helpful in diagnosis and prognostic evaluation of certain tumors as well as a possible diagnostic marker for theses neoplasms.

We have examined the expression of CD44 in benign and malignant neoplasms in NF1 patients to determine whether the differential expression of CD44, if any, correlates with infiltration or malignancy in these lesions. We have also undertaken an immunohistochemical assessment of the presence of functional wild type and mutant p53 protein in these tumors to elucidate whether or not p53 is also involved in the malignant transformation of neurofibroma.

Materials and methods

Twenty-eight benign and 16 malignant peripheral nerve sheath tumors were identified from the surgical pathology archives. Only specimens resected from patients with a known and documented clinical diagnosis of Neurofibromatosis Type I were selected for this study. Hematoxylin and eosin (H & E) stained sections along with any available special studies (S-100, etc.) were also reviewed to confirm the diagnosis. Forty-four tumors from 33 patients were selected and evaluated for immunoexpression of CD44, CD44 v6 and p53.

Antibodies

p53: Mouse monoclonal antibody, DO-7 (Novocastra Laboratories Ltd) is specific for human p53 protein, wild type and mutant forms. Dilution used: 1:100. Immunopositivity with this antibody has been correlated with altered expression of the p53 gene and is an accepted method of detecting p53 abnormalities.

P53 immuno expression was semi-quantitated using Image ProPlus Image Analysis System (Media Cybernetics, Silver Spring, MD). Three areas with maximal immunoreactivity were sampled from each case. A medium power (20X) field was video-captured and analyzed for nuclear staining. Data is expressed as the number of positive nuclei/20X field and categorized as follows: 0-10%, 10-30%, 30-60% and greater than 60% immunopositive nuclei.

CD44H: Mouse, anti-human CD44 monoclonal antibody that recognizes human standard CD44 and all protein isoforms. It is unable to distinguish splice variants. Dilution used: 1:100. (R and D Systems).

CD44v6: Anti-human CD44 variant 6, mouse monoclonal antibody that recognizes any protein containing the variant 6 exon. Dilution used: 1:100. (R and D Systems).

All specimens had been fixed in 10% formalin and embedded in paraffin. Sections were incubated for 30 minutes in primary antibody. After multiple rinses in phosphate buffered saline, sections were incubated in a biotinylated secondary antibody (Vector Laboratories, Inc., Burlingame, CA), followed by a streptavidin-complex reagent containing horseradish peroxidase

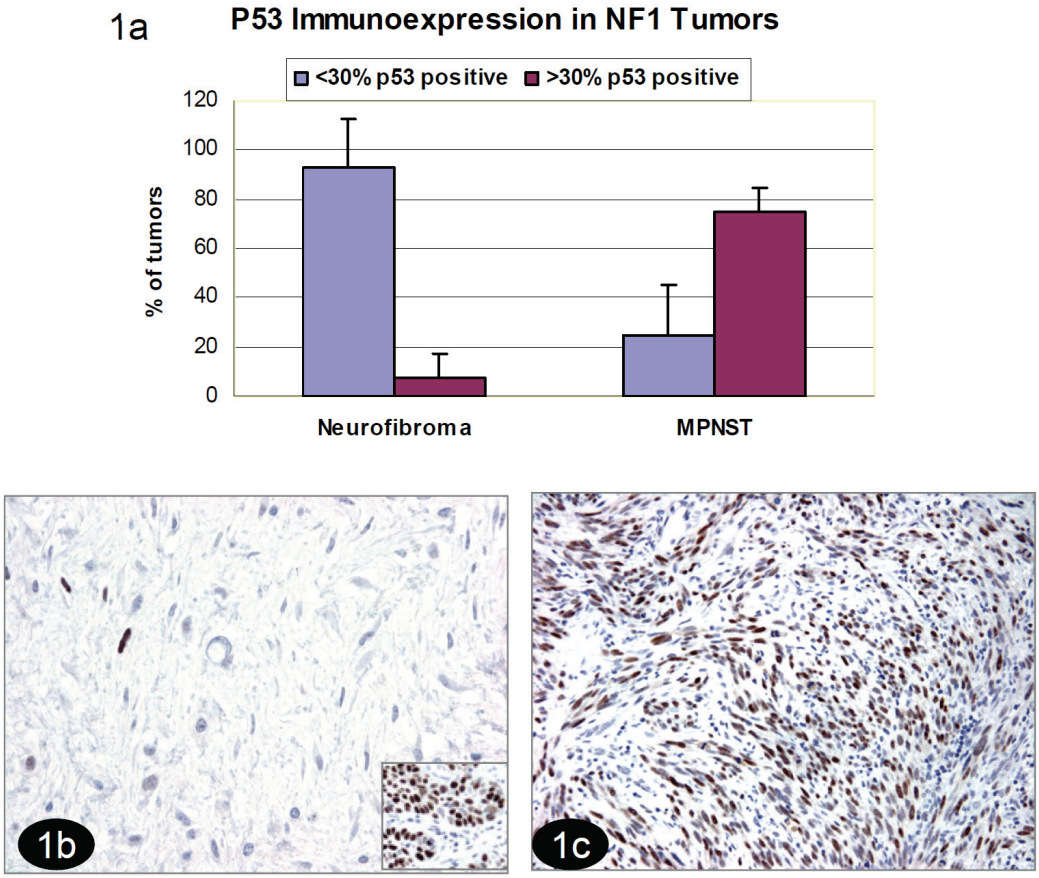

Figure 1. (a) Limited p53 immunoreactivity (less than 30%) was seen in 93% of benign neurofibroma, while 75% of MPNST showed moderate to strong positivity (>30% positive nuclei). (b) Benign neurofibroma with scattered p53 positive nuclei. Original magnification 400x, CD44 immunoreaction, counterstained with hematoxylin. Inset: Positive control- Metastatic adenocarcinoma. (c) MPNST with greater than 70% p53 immunoreactivity. Original magnification 400x, CD44 immunoreaction, counterstained with hematoxylin.

(Zymed Laboratories, Inc., South San Francisco, CA). Slides were rinsed and incubated with the chromogen DAB (3,3'-diaminobenzidine) and counterstained with methyl green or hematoxylin. Lymphoid tissue, normal epithelium (skin) and a known adenocarcinoma of the colon served as the positive controls for CD44, while the same tumor also served as a positive control for p53. Negative controls included either no primary antibody or nonspecific IgG applied to the sections.

Statistical analysis was performed with comparison between percentages of the individual groups using nonparametric t-test as well as chi-squared analysis. Statistical significance was defined as a p-value of less than 0.05.

Results

p53

Immunoreactivity for p53 was seen as discrete nuclear staining. Twenty six of the 28 benign neurofibroma (93%) showed limited (< 30%) p53 immunoreactivity. Two cases (7%) did show between 30-60% p53 staining. In contrast, 12 of 16 (75%) of MPNST showed moderate to strong positivity (>30% positive nuclei). Of the 30 lesions that had < 30% positivity 26 (87%) were neurofibroma and 4 (13%) were MPNST. Twelve of 14 (86%) of the cases with >30% immunoreactivity were MPNST and 2 (14%) were neurofibroma. This data shows a strong positive correlation between p53 immunoreactivity and MPNST ($p<0.001$) (**Figure 1a-c**).

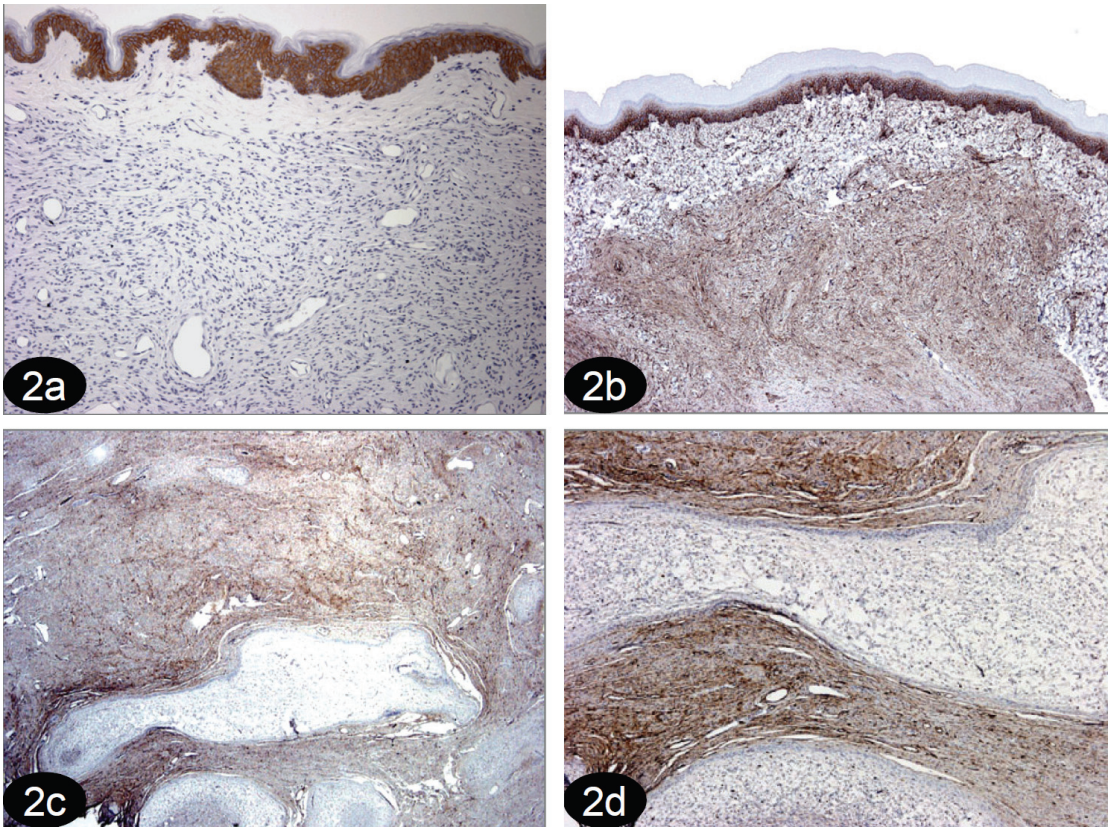

Figure 2. (a) CD44v6 positivity in normal epithelium (serving as an internal control) and absence of immunoreactivity in the underlying cutaneous neurofibroma. Original magnification 40x, CD44v6 immunoreaction, counterstained with hematoxylin. (b) CD44 staining in cutaneous neurofibroma. Note the poorly defined margin of the tumor, and immunoreactivity of normal epithelium. Original magnification 40x, CD44 immunoreaction, counterstained with hematoxylin. (c and d) Plexiform neurofibroma demonstrating minimal staining within the 'nodular' portions of the tumor, while the more cellular, loose, infiltrative, "non-confined" portions of the tumors tumor surrounding these nodules were markedly positive. Original magnifications 40x, and 200x, CD44 immunoreaction, counterstained with hematoxylin.

CD44

CD44v6 splice variant did not stain any of the tumors examined although epidermal positivity was seen (**Figure 2a**).

Eight of 11 (73%) of locally infiltrative cutaneous neurofibroma were diffusely positive for CD44, both in the tumor cells and the overlying epidermis (the latter providing an internal positive control). The remaining 3 cases (27%) were only focally positive within the tumor cells. Widespread positivity was seen in 13 of 16 (81%) of MPNST examined. The remaining 3 cases (19%) were either only focally positive or negative. Thus CD44 expression could not be correlated with the benign or malignant status of the tumors.

The 17 (non-cutaneous) benign tumors examined, in general, showed minimal or only focal immunoreactivity for CD44. However 3 of 5 plexiform neurofibroma and all cutaneous tumors with a tumor nodule (n=5) showed an unusual pattern of immunoreactivity. Tumors that were well-defined and nodular or appeared "well encapsulated," were minimally positive for CD44. Subcutaneous tumors that were poorly defined (**Figure 2b**) and even with a small focus of tumor were strongly immunoreactive. Plexiform neurofibroma demonstrated a similar pattern. The 'nodular' portions of the tumor were often negative while the more cellular, loose, infiltrative, "non-confined" portions of the tumors tumor surrounding these nodules were markedly positive (**Figure 2c** and **d**).

Discussion

Malignant peripheral nerve sheath tumors (MPNST) are aggressive soft tissue tumors that occur either sporadically or in patients with neurofibromatosis type 1. The malignant transformation of the benign neurofibroma to MPNST is not completely understood at the molecular level. Not surprisingly, patients with distant metastasis have a significantly worse outcome. In several series, the estimated 10-year disease-specific survival for patients presenting with metastatic disease was approximately 8% versus 30% for patients presenting with primary disease and 25 % for patients presenting with recurrent disease, despite the use of conventional therapy [24, 25]. This dismal prognosis highlights the importance of identifying patients with neurofibroma that may progress to MPNST as well as those with localized MPNST who are at high risk for metastatic development. We therefore investigated CD44 and p53 expression in benign and malignant peripheral nerve sheath tumors and found that malignant transformation from neurofibroma to MPNST occurs in part to the inactivation of p53 tumor suppressor gene and upregulation of CD44 adhesion molecule.

Mutations in the p53 tumor suppressor gene appear to result in changes in the molecular structure of the protein, such that there is increased stability and higher steady-state level of the protein. Thus overexpression of the protein as detected by Immunohistochemistry, correlates with mutations of the p53 gene. This correlation has been demonstrated for a number of tumors including breast, lung, ovary, endometrium and gastrointestinal neoplasms [26-39]. There is increasing evidence that mutations in genes other than the NF1 gene contribute to the development of malignancies in patients with NF1 and p53 has been suggested to participate in the malignant transformation of tumors these patients [9-11, 13, 40]. There is also evidence that increased p53 immunoreactivity may correlate adversely with prognosis [41].

CD44 is a cell adhesion molecule that promotes cell-extracellular matrix protein interactions. Both CD44 and its splice variants have been shown to play a role in both infiltration and metastasis in various malignancies, including those of the central nervous system [17, 18, 21-23, 42-46]. The marked positivity for CD44 seen in most MPNST is in favor of a role for this molecule in infiltration and possibly metastasis. In our series we had a single MPNST metastatic to the regional lymph nodes. This tumor was intensely CD44 immunoreactive, with positive staining of almost every tumor cell. Additionally, the pattern of immunoreactivity in locally infiltrative cutaneous neurofibroma which histologically have very poorly defined margins, combined with the immunoreactivity seen in "nonencapsulated" areas of plexiform and cutaneous tumors further supports this role in infiltration and progression. In summary CD44 immunoreactivity is most intense in infiltrative and nonencapsulated tumors, irrespective of benign or malignant status.

In conclusion the present study defines a correlation between p53 overexpression and malignancy in NF1. A marked increase in the nuclear expression of mutant p53 in MPNST was seen in 12/16 cases (75%). Additionally, p53 positive nuclei were also seen in some benign neurofibroma, however, in significantly lower numbers. These findings support a role for p53 mutations in the malignant transformation of benign NF1 tumors, although other molecular factors are also involved in this process.

Additionally the study describes the immunoexpression pattern of CD44, in that within the confines of encapsulated tumors expression is limited, while in poorly circumscribed neurofibroma CD44 expression is upregulated. CD44 was also strongly positive in invasive MPNST. This is thought to reflect the interaction of CD44+ tumor cells with extracellular matrix, hence facilitating infiltrative behavior.

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