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S100A6 preferentially labels type C nevus cells and nevic corpuscles: additional support for Schwannian differentiation of intradermal nevi

Background: Melanocytic nevi typically show a morphologic sequence of maturation from epithelioid "type A" cells to fusiform, Schwann cell-like "type C" cells with dermal descent. Nevi may also produce Wagner-Meissner-like structures (nevic corpuscles). Previous studies have shown that this maturation of intradermal nevi recapitulates intermediate stages in Schwann cell development. In intradermal nevi, we have evaluated the pattern of S100A6 protein, a form of S100 found in Schwann cells.
Methods: Formalin-fixed, paraffin-embedded archival tissues were evaluated by immunohistochemistry using antibodies specific for S100A6 and S100B in 38 intradermal nevi (IDN). Ten neurofibromas (NF), 3 Schwannomas (SCH), 2 palisaded and encapsulated neuromas (PEN), and 2 granular cell tumors (GCT) were included as positive controls since these lesions have large numbers of Schwann cells.
Results: Melanocytic nevi demonstrated preferential anti-S100A6 staining of "type C" cells (36/38; 28 strong, 8 weak) and nevic corpuscles (25/38; 19 strong, 6 weak) compared to "type A" cells (17/38; 17 weak) and "type B" cells (17/38; 4 strong, 13 weak). All NF, SCH, and PEN stained strongly with anti-S100A6. Both GCT were negative with anti-S100A6 but positive with anti-S100B.
Conclusions: The pattern of S100A6 expression in intradermal nevi further supports the hypothesis that maturation in these lesions recapitulates features of Schwann cell differentiation. The lack of S100A6 expression by both GCT suggests that these lesions have lost this feature of Schwann cells, which may play a role in their peculiar phenotypic appearance.

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Melanocytic nevi demonstrate morphologic "maturation" characterized by a progression from epithelioid "type A" cells in the papillary dermis to lymphocyte-like "type B" cells to Schwann-like "type C" cells with progressive descent in the dermis.[1,2] Over the past century, the origin of the type C nevus cell has been a topic of considerable debate. Unna considered the origin of dermal nevus cells to be derived from epidermal melanocytes by a dropping off process referred to as "*abtropfung*".[3] Yet, other investigators promoted the theory that at least some dermal nevus cells were derived from Schwann cells in the dermis, a pro-

cess referred to as "*hochsteigerung*" or ascending of the cells.[4,5]

Evidence in support of a melanocytic origin of dermal nevus cells is derived from ultrastructural, biochemical, and light microscopic observations. In 1965, Gottlieb et al. demonstrated the close resemblance of nevus cells to melanocytes by ultrastructural analysis.[6] In 1971, Thorne et al. demonstrated tyrosinase activity in type C nevus cells by electron microscopy using a modified DOPA reaction.[7] Moreover, age-related changes in intradermal nevi (IDN) also support a single histogenesis from melanocytes.[8–11]

IDN show terminal "maturation" along a Schwann cell differentiation pathway in progressing to type C nevus cells. Goovaerts et al. proposed that "atrophy" is a more appropriate term than maturation for this process, based on decrease in size and number of most cellular constituents, except for mitochondria and microfilaments.[12] Evidence for Schwannian differentiation comes from the close resemblance of type C nevus cells to Schwann cells by light and electron microscopy,[4,13–15] presence of pseudo-Meissnerian corpuscles (nevic corpuscles) in some IDN,[4,13,16,17] intimate relationship between type C nevus cells and complex networks of small unmyelinated axons,[4,18,19] and similarities in immunophenotype between type C nevus cells and Schwann cells.[17,20,21]

Immunohistochemical studies have shown that type C nevus cells recapitulate Schwann cells in an intermediate stage of differentiation, i.e. lack the ability to produce and maintain myelin. Aso et al. demonstrated expression of a Schwann cell-associated protein (AHMY-1), which reacted with P0 and P1 myelin proteins and myelin basic protein but not P2 myelin protein, in both type C nevus cells and nevic corpuscles (NC).[17] Some authors have shown that type C nevus cells do not express myelin basic protein, a feature of terminally differentiated Schwann cells, by immunohistochemistry.[22,23] Reed et al. showed that type C nevus cells and NC adopted an intermediate, "premyelinating/promyelinating" Schwann cell phenotype based on expression of low-affinity nerve growth factor receptor (p75-NGFR), neural cell adhesion molecule (N-CAM/CD56), and growth-associated phosphoprotein-43 (GAP-43).[21] Prieto et al. demonstrated the relationship of small axons to type C nevus cells and NC using an antibody to the intermediate filament peripherin;[24] however, the type C nevus cells and NC did not label with peripherin.[24,25] Argenyi et al. demonstrated strong p75-NGFR expression in NC, as well as in type C nevus cells, and suggested that nerve growth factor was important in development of NC, and that "neural differentiation" was a feature seen in some long-standing nevi.[26]

Ultrastructurally, type C nevus cells show similar features to spindle cells associated with NC, i.e. spindle cells possessing abundant cytoplasmic intermediate filaments, discontinuous basal lamina, and frequent pinocytotic vesicles.[17,27] NC have laminated cytoplasmic structures and, therefore, closely resemble Wagner-Meissner tactile bodies of the skin.[16,28,29]

S100 protein is strongly expressed by cells of neural crest origin, including melanocytes, Schwann cells, and NC.[30–34] Since the original isolation of S100 protein, a mixture of predominantly S100B and a lesser amount of S100A1, from bovine brain extracts by Moore in 1965,[35] several other S100 calcium-binding proteins have been discovered.[36,37] S100A6 protein, a.k.a. calcyclin, was discovered in 1986 by Calabretta et al.[38] This protein has been isolated from a variety of normal cell types, including melanocytes, Schwann cells and Schwann-like cells, Langerhans' cells, dermal dendrocytes, some glandular epithelium, and keratinocytes (weak).[39–43] Some melanocytic nevi express S100A6 protein by immunohistochemistry.[44]

Since S100A6 protein has been reported in some melanocytic nevi and Schwann cells, we evaluated the pattern of S100A6 protein expression in IDN by immunohistochemistry to determine if the staining pattern supports terminal differentiation along a Schwann cell pathway. In addition, we evaluated a variety of neural tumors thought to have a prominent Schwann cell component to see if there was any difference in their expression of S100A6 protein.

Material and methods

Cases of IDN (38), neurofibroma (NF) (10), Schwannoma (SCH) (3), solitary circumscribed neuroma/palisaded encapsulated neuroma (PEN) (2), and granular cell tumor (GCT) (2) were retrieved from the Dermatopathology Service and Archives at the New York Hospital-Cornell University Weill Medical College during the period of July 1998 to July 1999. IDN that possessed spindled cells in the deep dermis or had NC were specifically sought for inclusion in the study.

Formalin-fixed, paraffin-embedded tissue sections, approximately 4 μ thick, were placed on charged (plus), gray-frosted, 75 μ capillary gap ChemMate/BioTek slides (Ventana Medical Systems Inc., Tuscon, AZ, USA). A 1-h capillary action-based immunohistochemical technique was employed as described previously.[45] The sections were deparaffinized, rehydrated and treated with pepsin for 10 min at 45°C. Endogenous phosphatases were blocked using glacial acetic acid (1%) for 10 min at room temperature. Primary antibodies to S100A6/clone CACY-100 (1:1000, mouse monoclonal; Sigma, St. Louis, MO, USA) and S100B (1:1000, rabbit polyclonal; Dako, Carpinteria, CA, USA) were applied to serial tissue sections. Bound primary antibodies were detected

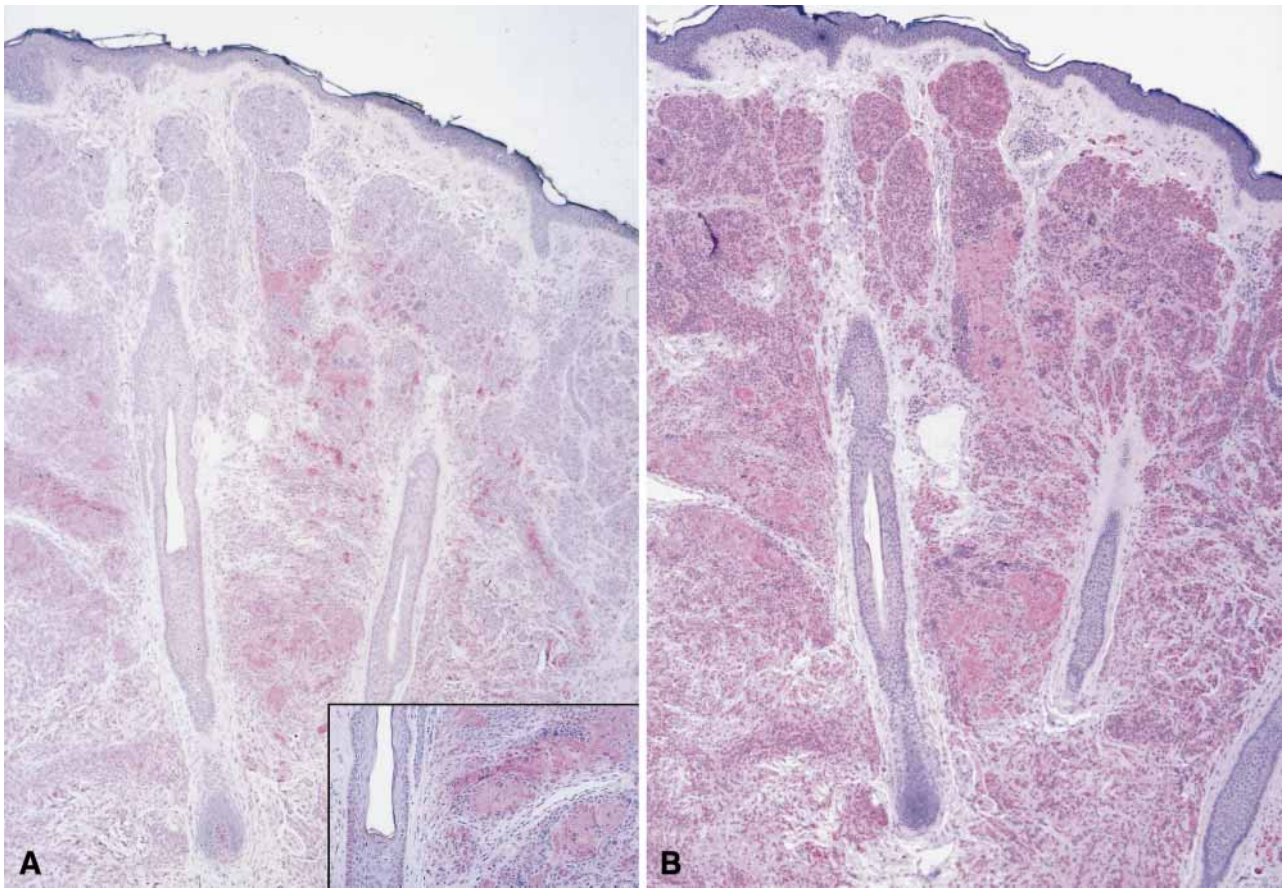

Fig. 1. Preferential labeling of type C nevus cells and nevic corpuscles (inset) with anti-S100A6 (A) compared to more diffuse labeling of type A-C cells and nevic corpuscles with anti-S100B (B).

using an streptavidin-alkaline phosphatase system. The complexes were visualized with red chromogen (SK-5100 kit; Vector Labs, Burlingame, CA, USA). Tissue sections were counterstained with hematoxylin.

The different tissues were compared with respect to types of cells stained and patterns of staining. Immunolabeling was determined to be present (+) or absent (−). Positive staining was then semiquantitatively graded as weak (1+) or strong (2+). The staining patterns were interpreted by two of the authors (J.A.R. and D.R.F.).

Chi-square analysis was performed using Sigma Stat software (Jandel Scientific, San Raphael, CA, USA) run on a PC. Statistical significance was assigned to a $p<0.05$ value.

Results

Thirty-six of 38 (95%) IDN showed S100A6 protein expression by type C nevus cells (28 strong, 8 weak) in the deep portion of the dermal component. In contrast, 17 of 38 (45%) type A (0 strong, 17 weak) and 17 of 38 (45%) type B (4 strong, 13 weak) nevus cells showed S100A6 protein expression in the upper and middle portions of the dermal component, respectively (Fig. 1). The preferential S100A6 labeling of type C nevus cells compared to types A and B nevus cells achieved statistical significance ($p<0.001$).

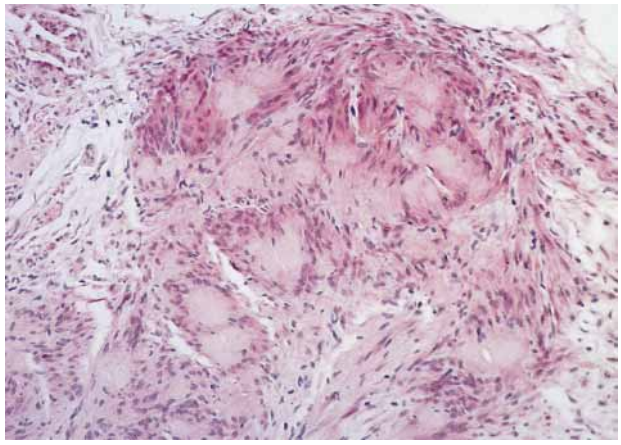

Fig. 2. Diffuse and strong labeling of Schwann cells and Verocay bodies in a Schwannoma.

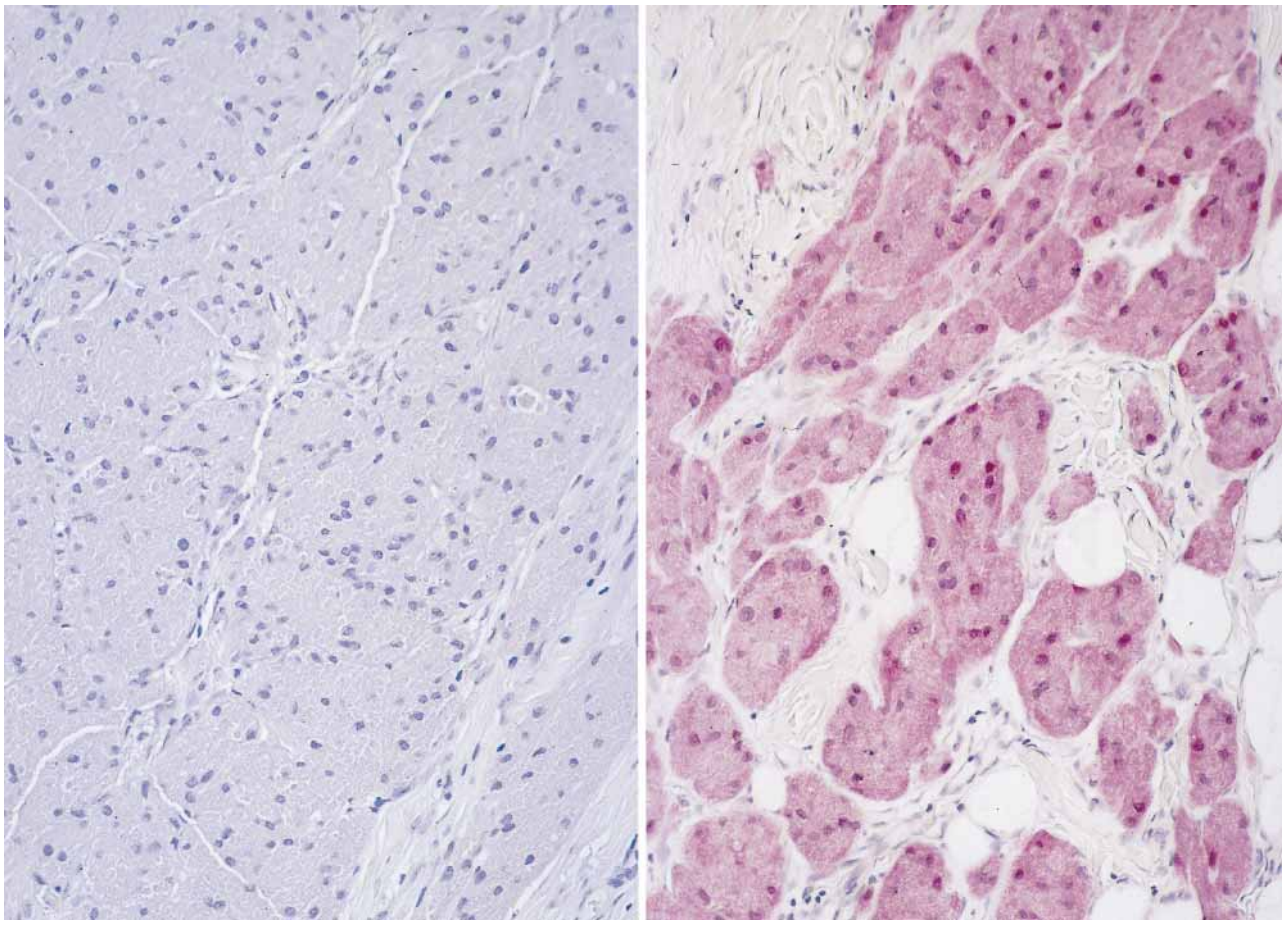

Fig. 3. Granular cell tumor showing absence of labeling with anti-S100A6 (left) but strong labeling with anti-S100B (right).

NC in 25 of 38 IDN (66%) showed positive staining (19 strong, 6 weak) with anti-S100A6 compared to type A (45%) or type B (45%) nevus cells (Fig. 1). This difference did not reach statistical significance ($p = 0.106$), probably due to the lack of NC in 11 of 38 (29%) IDN. Two cases with NC did not stain with anti-S100A6, but also did not have any staining with anti-S100B.

All 10 NF, 3 SCH, and 2 PEN demonstrated strong and diffuse positivity of the vast majority of spindled cells in the tumors (Fig. 2). Interestingly, both GCT did not label with anti-S100A6, but, as expected, showed strong and diffuse staining with anti-S100B (Fig. 3). On hematoxylin and eosin (H&E)-stained sections, the polygonal tumor cells had small central nuclei and abundant eosinophilic granular cytoplasm, as is typical of a GCT. The S100B protein expression excludes that either tumor is a fibrohistiocytic or smooth muscle tumor with granular cell change.

Discussion

Neural tumors, characterized by the presence of many Schwann cells, strongly expressed S100A6 calcium-binding protein in our study. This finding is not surprising considering previous reports of increased calcyclin gene expression in Schwann-like cells in neuroblastoma cell lines,[42] and Schwann cells of the rat nervous system.[43] The exception to these results was the absence of anti-S100A6 labeling of either GCT.

The histogenesis of the GCT has been debated for many years. In recent years, clinical, histological, immunohistochemical (S100B expression), and ultrastructural evidence has accumulated in support of a neural origin for the vast majority of GCT.[46–66] However, the exact neural cell from which the GCT is derived has remained elusive. Some observers have proposed that these tumors arise from the Schwann cell,[59–61] whereas other observers support an origin from the perineurial fibroblast,[67] or an undifferentiated mesenchymal cell.[68,69] We have demonstrated, albeit in only two cases, that S100A6, which is commonly expressed by Schwann cells, is not present in GCT. This immunophenotype finding in our GCT is in keeping with other immunophenotypic findings that are peculiar for terminally differentiated Schwann cells.[51,64,65,70,71] Additional studies includ-

ing a broader panel of antibodies on a larger number of GCT may shed light on whether these tumors are derived from modified Schwann cells or some, as yet, uncharacterized cell of the peripheral nerve sheath.

The preferential S100A6 expression of type C (vs. type A and B) nevus cells demonstrated in this study is additional support for terminal maturation of IDN along a Schwann cell pathway of differentiation. In addition, we demonstrated a tendency toward strong labeling of NC (Wagner-Meissner-like corpuscles) with anti-S100A6, a feature also consistent with Schwann cell differentiation.

The presence of some S100A6 labeling of type A and B nevus cells in IDN is clear evidence that melanocytes express S100A6 protein and is consistent with the previous observation by Böni et al.[39] The pattern of S100A6 protein expression compared to S100B expression in IDN lends further support to the opinion that dermal nevus cells are derived from nevomelanocytes in the epidermis. Moreover, some IDN, especially those of long-standing duration, demonstrate a predictable sequence of "maturation" in the dermis that terminates with type C nevus cells. These type C nevus cells share many phenotypic and ultrastructural features with an intermediate stage Schwann cell.[4,13–15,17,20–23]

In summary, we present compelling evidence, through differential patterns of expression of two S100 proteins, that the maturation of some melanocytic nevi recapitulates features of Schwann cell differentiation. In addition, this is the first report, to our knowledge, that demonstrates S100A6 protein expression in a variety of neural tumors of putative Schwann cell origin by immunohistochemistry. The absence of S100A6 protein expression by both GCT suggests that these lesions have lost this feature of Schwann cells, which is in keeping with other phenotypic findings that are peculiar for terminally differentiated Schwann cells.

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