gli-1 Oncogene Is Highly Expressed in Granulomatous Skin Disorders, Including Sarcoidosis, Granuloma Annulare, and Necrobiosis Lipoidica Diabeticorum

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Background: Sarcoidosis, which occurs most commonly in African American women, is a granulomatous multisystem disorder affecting the skin, lungs, and central nervous system. In a previous immunohistochemistry study of keloids, a scar granuloma stained highly positive for glioma-associated oncogene homologue (gli-1).

Observation: This observation led us to study whether gli-1, one of the vertebrate zinc finger transcription factor genes of the gli superfamily, is expressed in granulomatous skin disorders such as cutaneous sarcoidosis, granuloma annulare (GA), and necrobiosis lipoidica diabeticorum (NLD). Immunohistochemistry studies for gli-1 were performed on biopsy specimens from patients with cutaneous sarcoidosis, GA, and NLD. All sarcoid lesions were highly positive for gli-1 expression, and 75% of the cells demonstrated positivity with a stain intensity of 3 on a scale of 1 to 3. The gli-1 expression was confined to cutaneous granulomas. CD68 staining was highly positive in the sarcoid lesions as well. Similarly, GA and NLD lesions were uniformly positive for gli-1 expression.

Conclusions: We found that gli-1 is inappropriately expressed in granulomatous lesions of the skin such as cutaneous sarcoidosis, GA, and NLD. These findings provide a rationale for clinical trials of inhibitors of gli-1 signaling, including tacrolimus and sizolimus, for the treatment of cutaneous sarcoidosis and other granulomatous disorders of the skin.

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logue) oncogene and inhibitor of gli-1 signaling. In that study, we noted strong gli-1 expression in a suture-induced granuloma, and hypothesized that noninfectious granulomas may express gli-1 protein and that these granulomas may be treated with inhibitors of gli-1 signaling.

**METHODS**

Paraffin blocks of biopsy samples of 10 cutaneous sarcoidosis, 3 GA, and 5 NLD lesions were stained with antibodies against gli-1 oncogene, as previously performed on keloids. Briefly, 5-µm sections of formalin-fixed, paraffin-embedded tissue were tested for the presence of gli-1 using gli-1–specific antibodies (Santa Cruz Biotechnology, Santa Cruz, Calif) with an avidin-biotin complex technique and steam heat–induced antigen retrieval in a 1:20 ratio. An avidin-biotinylated enzyme complex kit (Dako LSAB2, Dako Corp, Carpinteria, Calif) was used in combination with the automated Dako Autostainer. Hematoxylin was used as a counterstain. Sarcoid lesions were stained with CD68 as well. The staining was done using an avidin-biotin–complex technique with pressure cooker heat–induced antigen retrieval and a Dako Autostainer. The percentage and intensity of positivity for gli-1 and CD68 were microscopically quantitated and recorded. The intensity of positivity was recorded on a 3-tiered scale graduated from 0 to 3 and the intensity of staining was recorded on a 4-tiered scale as follows: 0% to 5%, 0; 6% to 25%, 1; 26% to 50%, 2; 51% to 75%, 3; and 76% to 100%, 4. Statistical analyses were performed with the statistical package SPSS (SPSS Inc, Chicago, Ill).

**RESULTS**

All cutaneous sarcoid lesions showed high-level gli-1 expression in nearly all cells (Figure 1). Staining was predominantly cytoplasmic, similar to what has been observed in basal cell carcinoma. Cutaneous sarcoiids also demonstrated strong expression for CD68, which is consistent with the known strong expression of CD68 in this disorder (Figure 2). Strong gli-1 expression was also observed in lesions of GA (Figure 3) and NLD (Figure 4), ie, to areas of granulomas. There was no difference in intensity of staining between the 3 granulomatous disorders (Table). While there were differences between the 3 disorders in the percentage of cells that stained for gli-1, the difference was not significant (P=.24 by analysis of variance).

**COMMENT**

An oncogene that was initially characterized as a gene amplified in a human glioma, gli-1, hence the name gli-1, has been shown to transform cells in culture, and, more recently, to be involved in the pathogenesis of basal cell...
carcinoma. A transcriptional activator, gli-1 is downregulated by the PATCHED (PTC) gene, which is a receptor for the protein sonic hedgehog (Shh). The PTC gene represses gli-1 transcription, and when PTC is absent, as in basal cell nevus syndrome or sporadic basal cell carcinoma, gli-1 transcription is stimulated. Indeed, transgenic overexpression of gli-1 in mice leads to diffuse development of basal cell carcinoma.

We have previously found that gli-1 is highly expressed in keloids but not in hypertrophic scars. A suture-induced granuloma also stained positively for gli-1, suggesting that granulomas may also express gli-1. Mesenchymal cells in keloids have been shown to express CD68, a marker also commonly observed in granulomatous skin disease, suggesting that gli-1 may be expressed in granulomas as well as keloids. To determine whether this was the case, we stained specimens of cutaneous sarcoidosis, GA, and NLD. All specimens of granulomatous skin disorders stained strongly positive for gli-1. These results demonstrate a rationale for the use of inhibitors of gli-1 signaling, such as topical tacrolimus, in the treatment of granulomatous skin disorders. Indeed, a case report of a patient responding to tacrolimus (Protopic) for cutaneous sarcoidosis has been described. Further clinical trials of topical tacrolimus and other inhibitors of gli-1 signaling are warranted for the treatment of sarcoidosis, GA, and NLD.

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REFERENCES


ARCHIVES Web Quiz Winner

Congratulations to the winner of our November quiz, Reza Ghaderi, assistant professor of dermatology and dean of the Faculty of Medicine in Birjand, University of Medical Sciences, Iran. The correct answer to our November challenge was tularemia. For a complete discussion of this case, see the “Off-Center Fold” section in the December ARCHIVES (Hanson N, Hull C, Meyer L. Fever and lymphadenopathy in a farmer. Arch Dermatol. 2004;140:1531-1536).

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