Can C4AQO Decreased Frequency Be Considered a Genetic Marker for Vitiligo and Familial Melanoma?

G.		Orecchia
L.		Perfetti
M.		Cuccia
O.		Finco

Pavia

G. Orecchia, MD, L. Perfetti, MD, M. Cuccia, PhD, O. Finco, PhD, Dipartimento di Genetica e Microbiologia, dell'Università di Pavia, Via S. Epifanio 14, 27100 Pavia (Italy), Clinica Dermatologica, dell'Università di Pavia, P. le Golgi 2, 27100-Pavia (Italy)

Sir,

A decreased frequency of C4AQO has been found in both vitiligo and familial melanoma patients. This allele might be regarded as a genetic marker possibly acting as a resistance factor for both diseases. The serum complement proteins are an important part of the mammalian immune response being required for the lysis of antibody-targeted cells [1,2]. Some of these proteins (C2, Bf, C4), characterized by a high polymorphism, are encoded by genes representing the class III of the major histocompatibility complex (MHC).

Class III was reported to be involved in melanoma, with decreased Bf-FF and increased Bf-S alleles [3,4], and in familial melanoma, with a decreased C4AQO frequency [5]. Class III was referred to be involved also in sporadic vitiligo, with a decreased C4AQO frequency [6].

These observations suggest a possible genetic connection between melanoma and vitiligo, and give support to the hypothesis, already proposed by some authors [7], who stated that 'there is a genetically determined tendency of some pigment cells to be destroyed and yield some form of vitiligo or to become transformed to melanoma cells'. These authors hypothesized an immunological process 'by which the presence of vitiligo can counteract the proliferation of melanoma cells'. Our two works [5, 6] should give credit to this hypothesis even if many points must be clarified: the possibility to find a common clue in such different phenomena (the uncontrolled proliferation of malignant melanocytes and the destruction of melanocytes) remains a matter for speculation.

Among the possible explanations we consider: (1) The protein encoded by C4AQO is less efficient than those encoded by other alleles: as a result, a decreased frequency of this allele leads to an above average efficiency of the immune system which would be able to contrast, even if partially, malignant cells and would be responsible for an erroneous destruction of the delicate normal melanocytes. This hypothesis is confirmed by a greater survival rate of the patients with

familial melanoma [8, 9]. (2) The protein encoded by C4AQO is more efficient than those marked by other alleles: a decreased frequency of this allele (C4AQO) means an impaired immune surveillance and a consequent incapacity to control toxic factors responsible for the disappearance of melanocytes in vitiligo and for persistent stimulation resulting in malignant deviation. In this way multiple familial melanomas and their earlier occurrence [8, 9] in life are better explained. However it remains obscure what these noxious factors are: we cannot exclude a virus acting directly [10, 11] on melanocytes insufficiently protected by an inefficient immune system with an altered complement, or indirectly, by further damaging the immune system [12]. It must be stated that a reduced or increased activity of the complement system should interact with different targets and not just with melanocytes. Indeed vitiligo is known to be associated with different autoimmune diseases: such an association is not evident in familial melanoma but it should be searched for carefully to gain further support for our hypothesis. In fact a more active interaction between a particular complement phenotype and a specific antigenic target (normal or genetically abnormal melanocyte and also other tissues) could be expected since glycoproteins on the cell surface may offer a more or less accessible site for activation of C3 and C4 [1],

In conclusion, a genetical predisposition for familial melanoma [3, 4, 8] and for vitiligo [6, 13, 14] has been already demonstrated: our observation of reduced frequency of C4AQO in both diseases suggests the possibility of a common genetic marker, playing a role in the pathogenesis and/or in the evolution of these diseases and, in particular, acting as a resistance factor for familial melanoma and for vitiligo.

Acknowledgements

We are grateful to Dr. A.B. Lerner, MD, for his invitation to visit his department in Yale: it was a useful stimulus for our work. We are also grateful to Dr. M.T. Illeni of 1st. Nazionale per lo Studio e la Cura dei Tumori for kindly referring the patients with familial melanoma to us.

Research partially supported by Fondazione 'Pro Ricerca Derma-tologica'.

References

Porter RR: Complement polymorphism, the major histocompatibility complex and associated diseases: A speculation. *Mol Biol Med* 1983;1:161-168.

Porter RR: The molecular genetics of the components of complement and autoimmune diseases. *Biol Essays* 1984;6:261-264.

Milton GW, Balch CM, Shaw HM: Clinical characteristics; in Balch CM, Milton GW (eds): *Cutaneous melanoma*. Philadelphia, Lippincott, 1985, pp 13-28.

Budowle B, Barger BO, Balches CM, et al: Associations of properdin factor B with melanoma. *Can J Genet Cytol* 1982;5:247-251.

De Paoli F, Cuccia Belvedere M, Finco O, Illeni MT, Pellegris G, Cascinelli N: C4 and Bf polymorphism in familial malignant melanoma. *Med Biol Environ* 1988;16:307-315.

Orecchia G, Martinetti M, Finco O, et al: Different genetic markers in early onset and adult onset of sporadic vitiligo. *J Invest Dermatol* 1989;92:495.

Lerner AB, Kirkwood JM: Vitiligo and melanoma: Can genetically abnormal melanocytes result in both vitiligo and melanoma within a single family? *J Am Acad Dermatol* 1984;11:696-701.

Kopf AW, Mintzis M, Robson W, et al: Familial malignant melanoma. *Cutis* 1976;17:873-876.

Bork K, Brauner W, Naeve A: Increased frequency of multiple familial melanomas in hereditary familial melanoma. *Dermatologica* 1981;162:191-196.

Birkmayer GD , Balada BR, Miller F: Oncorna-viral information in human melanoma. Eur J Cancer 1974;10:419-424.

Parsons PG , Goss P , Pope JH: Detection in human melanoma cells lines of particles with some properties in common with RNA tumor viruses. Int J Cancer 1974;13:606-618.

Riley V, Spackman D: Melanoma enhancement by viral induced stress. Pigment Cell 1976;2:163-173.

Haider RM, Grimes PE, Cowan CA, et al: Childhood vitiligo. J Am Acad Dermatol 1987;16:948-954.

Foley LM, LoweNJ, Misheloff E, etal: Association of HLA-DR 4 with vitiligo. J Am Acad Dermatol 1983;8:39-40.

Hereditary Angioedema and Oral Contraception

To the Editor

Hereditary angioedema (HAE) is a rare autosomal dominant disorder characterized by a quantitative or functional deficiency of C1 esterase inhibitor (C1-INH) [1]. Attacks of angioedema may be induced by a variety of factors, such as tissue trauma, infection, anxiety, and fatigue [1]. The condition apparently is further influenced by sexual hormones [2-4].

Case Report. A 20-year-old previously healthy woman was given Diane® (containing 0.035 mg ethinyl estradiol and 2 mg cyproterone acetate) as treatment for acne. Three weeks after institution of the therapy she experienced attacks of poorly circumscribed, nonpitting and nonpruritic cutaneous swellings, along with occasional abdominal pain. The edema involved particularly the extremities, the trunk and further pressure-exposed sites. The episodes lasted for up to 3 days and occurred weekly. After 2 months she changed to Trinordiol® (containing 0.05-0.125 mg levonorgestrel and 0.03-0.04 mg ethinyl estradiol) as oral contraceptive agent (OCA), but attacks persisted. She was therefore given Lutényl® (containing 5 mg of norgestrel acetate) and she was free of symptoms until she discontinued OCA 2 months later.

Responses to repeated pressure challenges were all the time negative. Extensive laboratory investigations, including search for autoantibodies, did not reveal any abnormalities, except of the complement profile (table 1).