Giant Cells: Contradiction to Two-Hit Model of Tuber Formation?

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Received February 16, 2005; accepted March 8, 2005

SUMMARY

1. Tuberous sclerosis (TSC) is an autosomal dominant disease characterized by the formation of hamartomatous lesions in many organs, including brain, heart or kidneys. It has been found that TSC is caused by the mutation in one of two tumor suppressor genes: \textit{TSC1} or \textit{TSC2}, encoding hamartin and tuberin, respectively.

2. According to Knudson’s two-hit model of tumorigenesis, second-hit mutation and resulting loss of heterozygosity (LOH) of a tumor suppressor gene is necessary for tumor formation. In fact, LOH is commonly found in several types of hamartomas formed in the process of tuberous sclerosis, but, interestingly, not in brain lesions, containing characteristic giant cells.

3. In the present paper we review literature covering origination of giant cells and present several hypotheses explaining why in spite of the presence of hamartin and tuberin, brain lesions form in TSC patients.

KEY WORDS: giant cells; loss of heterozygosity; SEGA.

INTRODUCTION

Hamartomatous brain lesions, such as cortical tubers, subependymal nodules (SEMs) or subependymal giant cell astrocytomas (SEGAs) are a hallmark of tuberous sclerosis complex (TSC), an autosomal dominant genetic disorder with a high sporadic case rate. So far it has been elucidated that TSC occurs due to mutations in either of two genes, \textit{TSC1} on chromosome 9q34 (van Slegtenhorst \textit{et al.}, 1997) or \textit{TSC2} on 16p13 (European Tuberous Sclerosis Consortium, 1993), encoding hamartin and tuberin, respectively. Formation of tubers and nodules occurs mainly during brain development, and seems to be nearly complete at the time of birth. It has been reported that cortical tubers and subependymal nodules are present in 19 and 31 weeks.
gestation fetus (Park et al., 1997; Chou and Chou, 1989). Cortical tubers expand the gyri and cover the margin between the gray and white matter. Tubers are only occasionally seen in the cerebellum. Their calcification is commonly found, changing the tuber into a hard structure (thus, the name of the disease: “tuberous sclerosis”). Less frequently cortical tubers can degenerate into cystic lesions, which is not however connected with malignant transformation. Tubers can be limited to the cortex or the subcortical white matter. Originally, cortical tubers were believed to be pathognomonic, but according to current findings distinguishing these tubers from isolated cortical dysplasia on the basis of radiographic brain imaging and histological studies is difficult, although possible, at least in typical cases (Yagishita and Arai, 1999).

Subependymal nodules (SENs) are the most common brain lesions, which appear in about 90% of TSC cases. They are covered with a thin ependymal layer and contain elongated or swollen glial cells and their processes, giant or multinucleated cells, and sometimes, calcium depositions, although they are rarely calcified in the first year of life. SENs do not grow, but calcify progressively. By the age of 20, most of them are calcified.

SEGAs, whose incidence in TSC is about 5–15%, differ from subependymal nodules in their size and tendency to enlarge, which results in the clinical presentation of hydrocephalus. It is assumed that lesions greater than 12 mm are classified as SEGAs. The most important criterion of differentiation, however, is progressive enlargement of a lesion. Such a change in tumor size may lead to an increase of intracranial pressure, and result in significant morbidity and mortality. Differentiation between SENs and SEGAs is best performed on the basis of MRI investigation.

Cortical tubers are benign, while one malignant case of SEGA has been recorded (Telfeian et al., 2004). From our previous observations we hypothesize that subependymal nodules may grow and differentiate into SEGAs (Roszkowski et al., 1995). Nevertheless, even benign brain lesions in TSC lead to seizures, mental retardation and autism (Jozwiak et al., 1998). Pathogenesis of brain lesions in TSC is uncertain, and much effort is currently being put into identifying molecular and developmental mechanisms leading to the appearance of characteristic giant cells, found in the tubers, SENs and SEGAs. Because of numerous immunohistochemical and ultrastructural similarities (Jay et al., 1993; Bender and Yunis, 1980; Chou and Chou, 1989; Hirose et al., 1995), it has been hypothesized that giant cells in tubers and SEGAs share the same profile of differentiation and may be of the same cellular lineage (Lee et al., 2003).

HISTOLOGICAL EVALUATION OF GIANT CELLS

In histological evaluation of TSC brain lesions at least three cell populations can be identified: astrocytes, dysmorphic neurons, and giant cells, the last type being the characteristic for tuberous sclerosis. Many of the abnormally shaped neurons are stellate or multipolar cells not characteristic of normal cortex. Eosinophilic giant cells, which extend short thickened processes, are five to ten times as large as normal neurons. The first ultrastructural research on giant cells from a subependymal tumor and a cortical tuber argued for their astrocytic origin (Trombley and Mirra, 1981), as