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Original contribution

A unifying concept of trophoblastic differentiation and malignancy defined by biomarker expression

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Summary Several trophoblast phenotypes, including cytotrophoblast, syncytiotrophoblast, and extravillous trophoblast, emerge during gestation. To clarify the lineage relationship between these subtypes, we profiled p63 localization in developing and term placental tissue, as well as in trophoblastic tumors, using antibodies specific to full-length (TAp63) and one against all p63 isoforms (TAp63 and ΔNp63). Localization of p63 was compared with that of biomarkers of proliferation and trophoblastic differentiation, including mib-1, inhibin, and MelCAM. In early gestation, p63 was localized principally to villous cytotrophoblast after contact with the villous mesenchyme, absent in the trophoblast columns, and early implantation trophoblast. In the maturing placenta, intraplacental perivillous fibrin correlated with the emergence of a p63-positive "transitional" (vacuolated) extravillous trophoblast from cytotrophoblast, which differentiated further into a "mature" p63-negative extravillous trophoblast. The same lineage pathway emerged from entrapped villi on the chorionic membrane. Virtually all p63 immunopositivity was attributed to dominant-negative p63. The immunophenotypic patterns seen in the immature and mature placenta permit the resolution of all trophoblastic phenotypes within 3 lineage pathways of cytotrophoblast differentiation, including cytotrophoblast-to-trophoblast column/implantation site, cytotrophoblast-to-syncytiotrophoblast, and cytotrophoblast-to-mature extravillous trophoblast. In the latter pathway, a transitional (vacuolated) p63-positive extravillous trophoblast emerges from and links cytotrophoblast to mature extravillous trophoblast in intraplacental fibrin, chorionic membrane, and basal plate. The placental trophoblast is thus resolved within this continuum of differentiation. Terms such as *transitional* and *mature* extravillous trophoblast are proposed to reflect the differentiation phases of this unique epithelium. p63 staining patterns in trophoblastic tumors reflect timing of neoplastic transformation during trophoblastic differentiation.

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1. Introduction

In recent years, significant advances have been made in our understanding of early placental development, specifically trophoblastic differentiation and the classification of neoplasms derived from this epithelium. In 1979, the discovery of 2 genetically distinct hydatidiform moles answered a fundamental question of not only molar pathogenesis but also the mechanisms underlying aggressive behavior [1,2]. The complete mole, shown to be derived entirely from the male chromosomes, took center stage as a neoplasm that carried most of the risk of a malignant (choriocarcinoma) outcome [3]. In the early 1990s, early forms of this neoplasm were appreciated in the form of "early complete moles" [4,5]. Subsequently, discovery of paternally imprinted (inactivated) genes resulted in relatively simple immunohistochemical assays that would discriminate early complete moles from normal gestations [6,7]. In

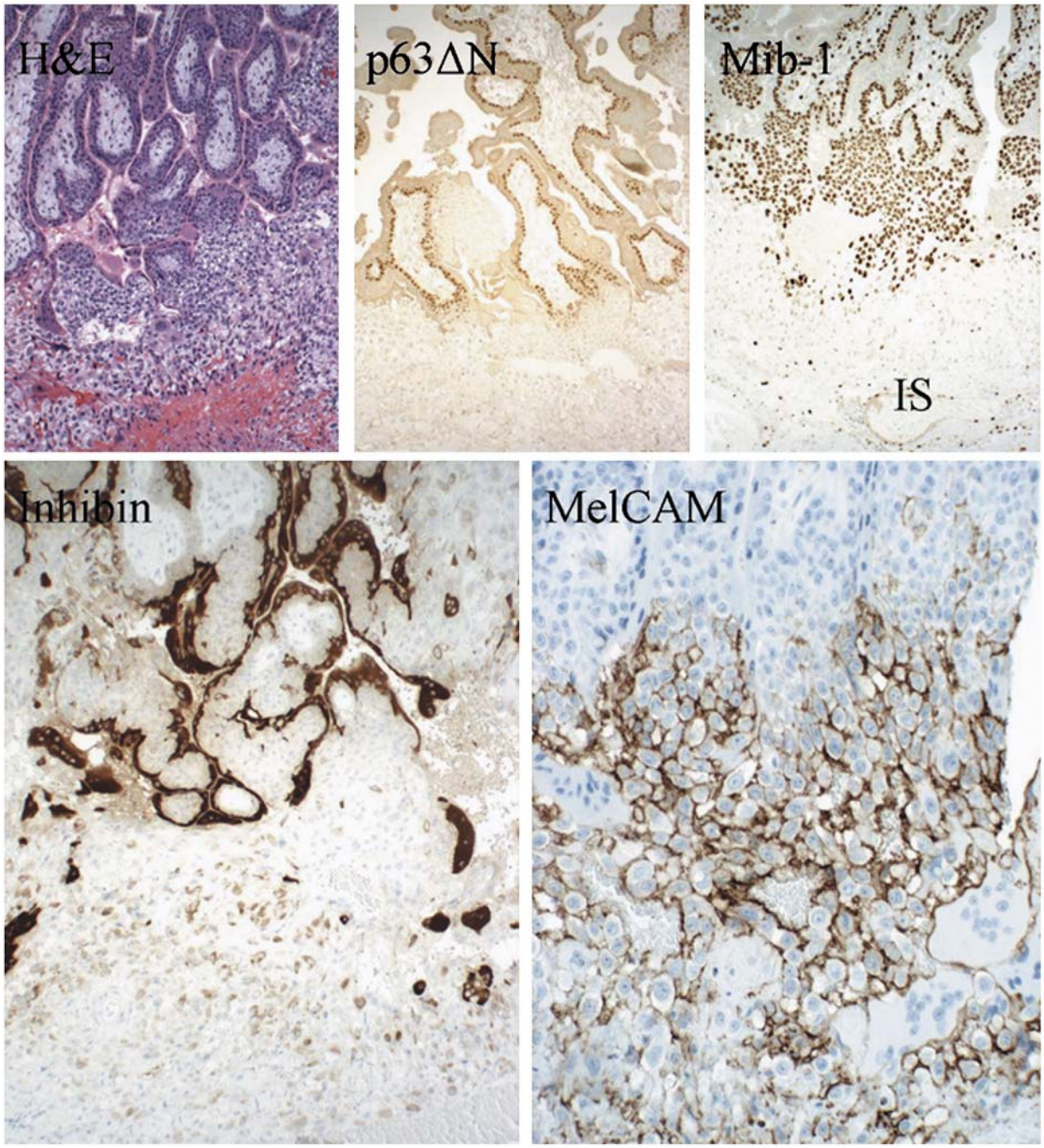

Fig. 1 Early trophoblastic column development (gestational age, 6 weeks): The columns are contiguous with the villous cytotrophoblast. Note the abrupt diminution in p63 immunostaining with column stratification, the latter associated with MelCAM expression. Mib-1 staining highlights both cytotrophoblast and columns, and diminishes rapidly in the implantation site (IS) beneath. H&E, hematoxylin-eosin.