Integrin α6 variants and colorectal cancer

I read with interest the study by De Archangelis *et al*[1] on the protective role of hemidesmosomes against colitis and colorectal cancer using genetically modified mouse integrin α6 subunit mutant models. I was however surprised to read that, based on their observations with these α6 mutant mice, the authors concluded that the α6β4 integrin can be classified as a tumour suppressor in the colon. Indeed, earlier studies have reported that in carcinomas, α6β4 can be released from hemidesmosomes to become associated with microfilament-associated cell motility adhesomes and, consequently, engage in various signal transduction pathways that contribute to tumour progression.[2 3] While it is recognised that the roles of α6β4 may be dependent on the tissue-context as underlined by the authors, it remains increasingly evident that the alternative messenger RNA splicing of the α6 subunit constitutes a key-contributing factor for the definition of the function of α6β4 in determining the fate of cancer cells,[4] including colorectal cancer cells.[5]

First, it is noteworthy that both α6 subunits are normally expressed in the

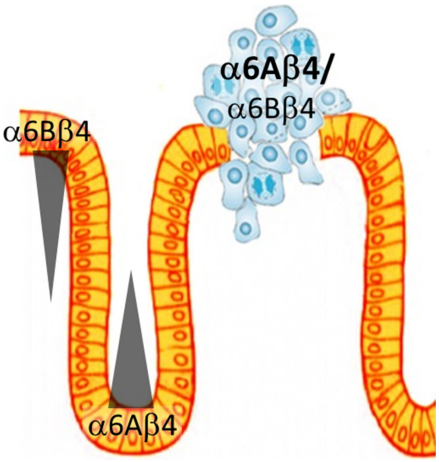

Figure 1 Schematic view of the colonic epithelium showing the differential expression of integrin α6β4 forms in the normal mucosa and in tumours. Under normal conditions, the α6A subunit is located in the proliferative cells of the gland while α6B is confined to the quiescent upper gland and surface epithelial cells.[5] In colorectal tumours, total α6β4 expression increases as its α6Aβ4 form.[5 8]

intestinal epithelium but in distinct compartments, α6A being found in the proliferative cells of the glands in both the small and large intestine while α6B is restricted to the quiescent/differentiated cells located on the villus and surface epithelium (figure 1).[5 6] Second, the expression of the α6β4 receptor is increased in colorectal cancer cells[5 7] and it is in fact its pro-proliferative α6Aβ4 form that is found to be largely expressed under this context,[8] whereas its α6Bβ4 counterpart appears to exert antiproliferative influences.[5] Altogether, these data indicate that α6β4 performs distinct functions in intestinal and colonic cells according to the specific α6 (A or B) splicing variant that constitutes the heterodimeric receptor.

In relation to these previously reported observations, one should also consider the likelihood that an abolition/loss of the α6β4 heterodimer in the gut epithelium favours compensatory cell–matrix interactions through other receptors such as the pro-proliferative 37/67-laminin receptor[9] and other previously identified pro-proliferative integrins,[10] which, singly or in combination, may contribute to the complex phenotype that has been observed in the experimental mouse mutant models described.[1]

In this context, the colon tumorigenesis observed in mice carrying a total gut epithelial-specific deletion of the α6 integrin subunits may need to be interpreted with caution.

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