

Integrin $\alpha 6$ 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 $\alpha 6$ subunit mutant models. I was however surprised to read that, based on their observations with these $\alpha 6$ mutant mice, the authors concluded that the $\alpha 6\beta 4$ integrin can be classified as a tumour suppressor in the colon. Indeed, earlier studies have reported that in carcinomas, $\alpha 6\beta 4$ 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 $\alpha 6\beta 4$ may be dependent on the tissue-context as underlined by the authors, it remains increasingly evident that the alternative messenger RNA splicing of the $\alpha 6$ subunit constitutes a key-contributing factor for the definition of the function of $\alpha 6\beta 4$ in determining the fate of cancer cells,⁴ including colorectal cancer cells.⁵

First, it is noteworthy that both $\alpha 6$ subunits are normally expressed in the

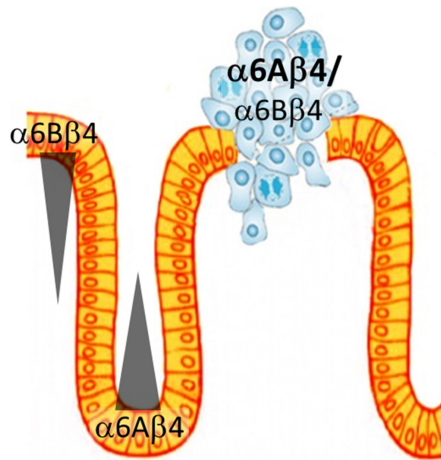


Figure 1 Schematic view of the colonic epithelium showing the differential expression of integrin $\alpha 6\beta 4$ forms in the normal mucosa and in tumours. Under normal conditions, the $\alpha 6A$ subunit is located in the proliferative cells of the gland while $\alpha 6B$ is confined to the quiescent upper gland and surface epithelial cells.⁵ In colorectal tumours, total $\alpha 6\beta 4$ expression increases as its $\alpha 6A\beta 4$ form.^{5,8}

intestinal epithelium but in distinct compartments, $\alpha 6A$ being found in the proliferative cells of the glands in both the small and large intestine while $\alpha 6B$ is restricted to the quiescent/differentiated cells located on the villus and surface epithelium (figure 1).^{5,6} Second, the expression of the $\alpha 6\beta 4$ receptor is increased in colorectal cancer cells^{5,7} and it is in fact its pro-proliferative $\alpha 6A\beta 4$ form that is found to be largely expressed under this context,⁸ whereas its $\alpha 6B\beta 4$ counterpart appears to exert antiproliferative influences.⁵ Altogether, these data indicate that $\alpha 6\beta 4$ performs distinct functions in intestinal and colonic cells according to the specific $\alpha 6$ (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 $\alpha 6\beta 4$ heterodimer in the

gut epithelium favours compensatory cell–matrix interactions through other receptors such as the pro-proliferative 37/67-laminin receptor⁹ 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 $\alpha 6$ integrin subunits may need to be interpreted with caution.

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