

# Integrin $\alpha 6\beta 4$ in Colorectal Cancer

Subjects: **Oncology**

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Integrin  $\alpha 6\beta 4$  is one of the main laminin receptors and is primarily expressed by epithelial cells as an active component of hemidesmosomes. In this article, after a brief summary about integrins in the gut epithelium in general, I review the knowledge and clinical potential of this receptor in human colorectal cancer (CRC) cells. Most CRC cells overexpress both  $\alpha 6$  and  $\beta 4$  subunits, *in situ* in primary tumours as well as in established CRC cell lines. The mechanisms that lead to overexpression have not yet been elucidated but clearly involve specific transcription factors such as MYC. From a functional point of view, one key element affecting CRC cell behaviour is the relocalization of  $\alpha 6\beta 4$  to the actin cytoskeleton, favouring a more migratory and anoikis-resistant phenotype.

colorectal cancer

integrin  $\alpha 6\beta 4$

ITGA6

ITGB4

alternative splicing

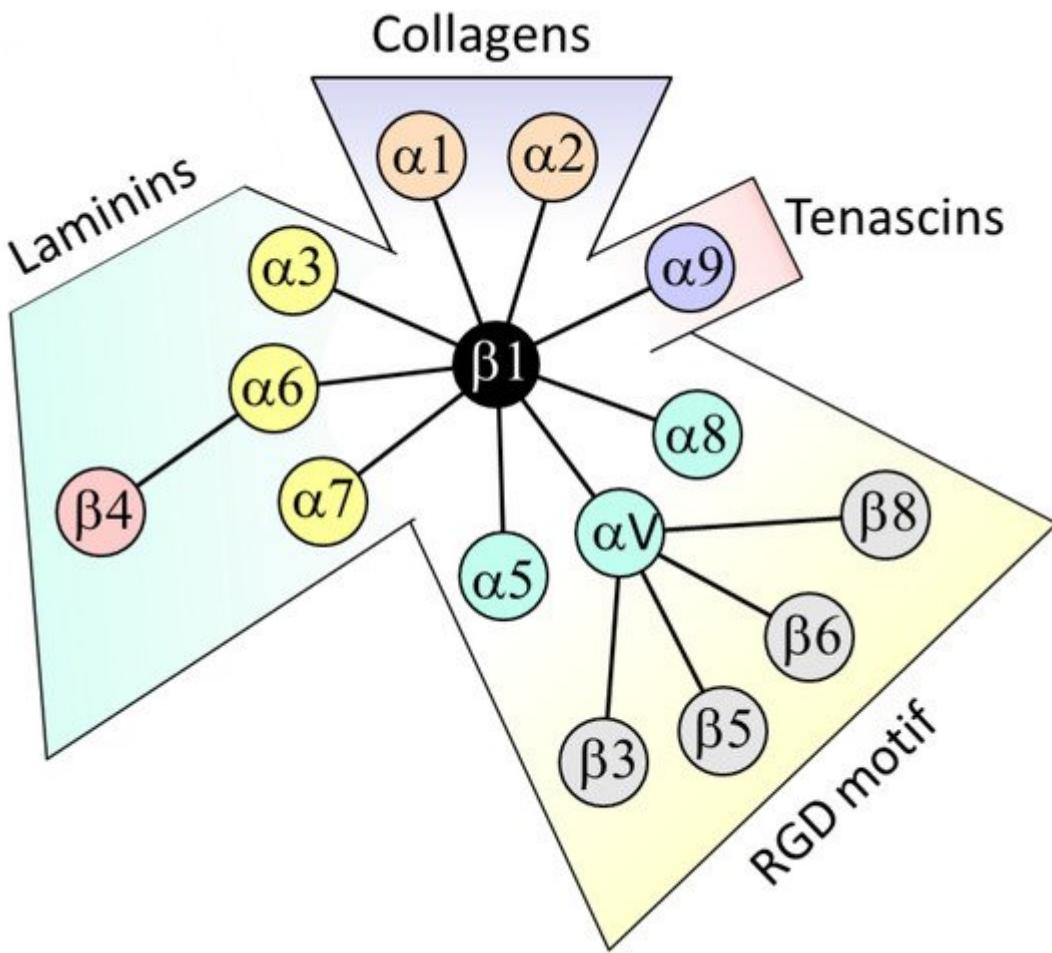
expression

function

biomarker

## 1. Introduction

Epithelial cells lie and attach to the basement membrane, a specialized network of extracellular matrix molecules that comprise specific collagens, proteoglycans and exclusive glycoproteins such as laminins as well as non-exclusive ones such as fibronectins. Cell adhesion is mediated by membrane receptors specific for these glycoproteins. In the intestine, there are a number of these receptors that have been identified for epithelial cells including dystroglycan and the 37/67 kDa laminin receptor [1] as well as many that belong to the integrin family [2][3]. Integrins are transmembrane  $\alpha\beta$  heterodimers that function as bidirectional signal transduction mediators acting as mechanosensors and participating in the regulation of main cell functions such as adhesion, migration, proliferation, survival and differentiation [4][5]. The gut epithelium expresses a wide variety of integrins as well as their corresponding ligands. **Figure 1** illustrates the various heterodimers identified and their extracellular ligands.



**Figure 1.** Integrins expressed in intestinal epithelial cells under normal or pathologic conditions. Integrins are classified according to their preferential ligands: collagens for  $\alpha 1/\alpha 2$  coupled to  $\beta 1$ , laminins for  $\alpha 3/\alpha 6/\alpha 7$  coupled to  $\beta 1$  or  $\beta 4$ , tenascin for  $\alpha 9\beta 1$  and RGD-containing ligands (fibronectin, osteopontin and vitronectin) for  $\alpha 5/\alpha 8$  coupled to  $\beta 1$  and  $\alpha V$  coupled to  $\beta 1/\beta 3/\beta 5/\beta 6/\beta 8$ .

It is noteworthy that while some of these integrins are mostly associated with the differentiated state in the intestinal epithelium cells such as  $\alpha 3\beta 1$  and  $\alpha 7\beta 1$ , many are predominantly expressed by the proliferative cells at the base of the epithelial cells of the crypts in both the small and large intestines [2][3][6] and, more importantly in the context of this review, in primary and/or metastatic colorectal cancer (CRC) cells. This has been well documented recently for the  $\alpha 1\beta 1$  integrin, a collagen receptor. While exclusively expressed in the proliferative compartment in the normal colon,  $\alpha 1\beta 1$  was found to be overexpressed in CRC primary tumour and cell lines [7][8] and knockdown of  $\alpha 1$  subunit expression resulted in the reduction of cell proliferation and tumour growth [9]. Integrin  $\alpha 9\beta 1$  is another interesting case. Expressed in the proliferative cells in the normal gut at the fetal stage but not in the adult, its resurgence in CRC cells both in primary tumours and in vitro is indicative of an oncofetal pattern of expression [10][11]. Two of the RGD-dependent integrins,  $\alpha 5\beta 1$  and  $\alpha V\beta 6$ , appear to contribute to the metastatic process of CRCs [12][13]. Interestingly, the  $\beta 6$  subunit is expressed at very low levels in epithelia under normal conditions but is detected in both CRC primary tumours and metastasis where it acts through various mechanisms and systems to promote cancer progression [12]. However, there are exceptions. For instance,  $\alpha 8\beta 1$  which has also been shown to

promote intestinal cell migration and proliferation in normal cells [14] appears to be no longer expressed by CRC cells [15]. Further investigation using normal intestinal cells revealed that this integrin acts as an anoikis-sensitizing trigger factor while the repression of its expression abolished this checkpoint [15]. Conversely, its reintroduction into CRC cells restores sensitivity to anoikis [15]. The  $\alpha V\beta 3$  integrin was also reported to act as an anoikis-sensitizing integrin for CRC cells [16][17]. These examples illustrate the crucial importance of the integrins as extracellular matrix molecule receptors involved in CRC cell progression, some susceptible to directly act in its promotion such as  $\alpha 1\beta 1$ ,  $\alpha 5\beta 1$  and  $\alpha V\beta 6$  while others act as preventive checkpoints such as  $\alpha 8\beta 1$  and  $\alpha V\beta 3$  or favour quiescence and differentiation rather than proliferation such as  $\alpha 3\beta 1$  and  $\alpha 7\beta 1$ . These effects are also context-dependent over the entire process, some acting at early stages of cancer development while, as mentioned above, others are more likely to act at a later stage such as in the metastatic process. Some integrins likely exert dual promoting/suppressive influence on CRC development and progression [18]. In this context, integrin  $\alpha 6\beta 4$  is one of the most intriguing cases since its different role in CRC may in part derive from its ability to assemble hemidesmosomes, a very stable cell-extracellular matrix adhesion structure, and its potential to modulate oncogenic cell signalling events when released from hemidesmosomes as well as its  $\alpha 6A/\alpha 6B$  variant composition. While it belongs to the laminin-binding integrin subset, which also includes  $\alpha 3\beta 1$ ,  $\alpha 6\beta 1$  and  $\alpha 7\beta 1$  [2][19][20],  $\alpha 6\beta 4$  is characterized by a large  $\beta$  subunit and its predominant expression is in parenchymal cells such as the epithelial cells that line the luminal surface of the colonic crypts.

## 2. $\beta 4$ Integrin Subunit (*ITGB4*) in CRC

### 2.1. Expression

The expression of the integrin  $\beta 4$  subunit in CRC has been the subject of a number of studies. While most of these have shown that  $\beta 4$  is uniformly distributed at the basal side of the colonic epithelium, its level of expression in primary CRC tumours was initially found to be quite variable depending on the study and antibody used, being found to be reduced or lost [21], maintained [22] or increased [23][24]. Increased expression was finally confirmed using a panel of distinct anti- $\beta 4$  antibodies and validated at the transcript level [25].

The use of this panel of anti- $\beta 4$  antibodies including two directed against extracellular epitopes and two targeting the cytoplasmic COOH-domain revealed interesting features. Indeed, in the normal small intestine and colon, cells of the crypts expressed a co-translationally processed form of  $\beta 4$  lacking the cytoplasmic terminal domain ( $\beta 4\text{ctd-}$ ) [26] so that only antibodies directed to the extracellular domain stained epithelial cells of the colonic crypts [25]. In contrast, the differentiated cells of the small intestinal villi and colonic surface epithelium expressed normal  $\beta 4\text{ctd+}$  suggesting that the  $\beta 4\text{ctd-}$  form is related to the proliferative and less differentiated cells of the renewing intestinal epithelium [25][26]. Unexpectedly, colonic cells from both primary CRC and established adenocarcinoma cell lines expressed the  $\beta 4\text{ctd+}$  form, suggesting that this processing of  $\beta 4$  is lost or at least downregulated in neoplastic cells [25]. The potential impact of this is addressed below.

### 2.2. Regulation of Expression

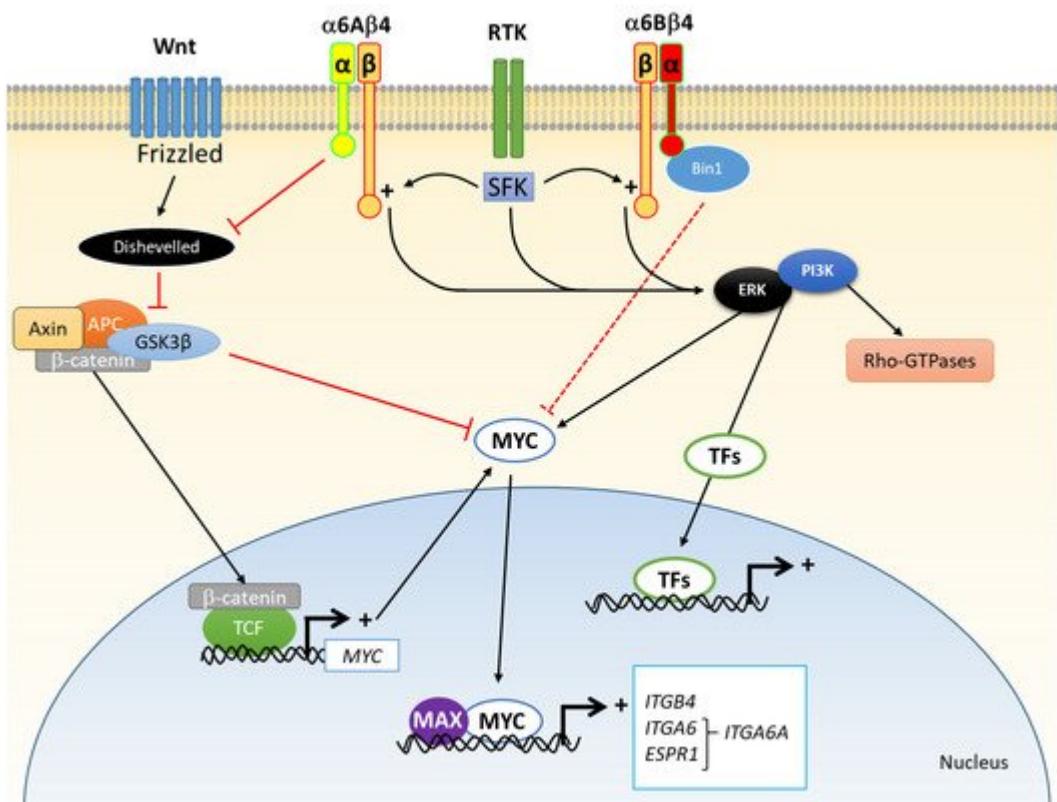
Integrin  $\beta 4$  subunit expression appears to be mainly regulated at the transcript level but the mechanism of its overexpression in CRC cells is still incompletely understood. There have been a number of studies that have reported specific potential interactions of transcription factors with the *ITGB4* promoter since its cloning [27] in a variety of cell types including RUNX1 [28], JUN [29] and KLF4 [30]. In CRC cells, MYC was the first transcription factor identified that promotes *ITGB4* transcription [25] but recent studies have found others such as ZKSCAN3 [31] and FOSL1 [32] that need to be considered. Epigenetic regulation of *ITGB4* expression has also been suggested after identification of microRNAs that may target the *ITGB4* transcript such as miR-21 [33] and miR-335-5p [32] as well as hypomethylation of the *ITGB4* promoter [32].

### 2.3. Change in Functionality

In normal epithelial cells, the  $\beta 4$  subunit is one of the key components of hemidesmosomes, a specialized adhesive structure found in epithelia. Most integrin  $\beta$  subunits bear short cytoplasmic domains smaller than 50 amino acids able to interact with actin filaments through cytoplasmic linker proteins such as talin and vinculin that are also used as scaffolding for the recruitment and activation of intracellular signalling pathways [34]. In contrast,  $\beta 4$  has a 1000 amino acid cytoplasmic domain composed of distinct sequences not found in other  $\beta$  integrins: a Calx $\beta$  motif adjacent to the plasma membrane, two pairs of fibronectin type III domains, a connecting segment and a COOH-terminal end domain [35]. In hemidesmosomes,  $\alpha 6\beta 4$  mediates the intracellular interaction with cytoskeletal keratins through various plakins such as plectin and the extracellular interaction with laminins, preferentially laminin-332 [35]. However, hemidesmosomes are dynamic structures that need to be dismantled to allow cell migration and other cell dynamic functions. There are a number of mechanisms that have been suggested for the release of  $\alpha 6\beta 4$  from the hemidesmosomes [18] mainly the phosphorylation of the  $\beta 4$  cytoplasmic tail in response to receptor tyrosine kinase activation by growth factors [18][36]. Upon release,  $\alpha 6\beta 4$  switches its association with cytokeratin to relocalize with actin filaments favouring the formation of motility structures [36]. In this context, it is worth mentioning that the processing of  $\beta 4$  into  $\beta 4\text{ctd}$ - in normal proliferating intestinal cells impairs the ability of  $\alpha 6\beta 4$  to bind to laminin [26], which by increasing susceptibility to anoikis may represent an additional checkpoint mechanism for preventing aberrations in the permanent cell population responsible for epithelial renewal in the intestine [37].

In carcinoma cells, numerous studies have demonstrated that  $\alpha 6\beta 4$  promotes cell motility and invasive behaviour rather than stable anchoring to the extracellular matrix via a mechanism related to the one used for cell migration in wound healing in normal cells [36]. Since the discovery that  $\alpha 6\beta 4$  promotes colonic carcinoma cell invasiveness by activating the PI3K pathway [38], there have been a number of studies that have contributed to better documenting the potential of integrin  $\alpha 6\beta 4$  to regulate multiple signal transduction cascades involved in the promotion of cell proliferation, migration, invasion and suppression of anoikis [18][36][39]. While I invite the reader to refer to these seminal reviews [18][36][39] for further details about the multiple signalling transduction cascades that can be activated by  $\alpha 6\beta 4$  upon binding to its ligand, a few crucial elements are worth mentioning herein in the context of colorectal cancer (Figure 2). First, is the ability of  $\alpha 6\beta 4$  to synergistically cooperate with oncogenic receptor tyrosine kinases such as those of the epidermal growth factor receptor family and c-Met, which via their downstream effectors, the Src family of kinases, trigger the phosphorylation of tyrosine residues in the cytoplasmic

domain of the  $\beta 4$  subunit to enhance the signal [34]. Second are the mechanisms by which  $\alpha 6\beta 4$  promote migration and invasion, which include the activation of the small GTPase RhoA and the up-regulation of the metastasis-associated protein S-100A4 [36]. Third is the apparent dual influence of  $\alpha 6\beta 4$  on cell survival. In most cell types, cell survival requires an  $\alpha 6\beta 4$ -dependent PI3K activation and blocking  $\alpha 6\beta 4$ -mediated adhesion trigger apoptosis [39]. However, using the RKO colon carcinoma cell line, Mercurio's team showed that the ability of  $\alpha 6\beta 4$  to promote or inhibit apoptosis depends on the p53 cell status. Furthermore, the loss of the  $\beta 4$  ctd- form in carcinoma cells, which strengthens  $\alpha 6\beta 4$ -laminin interactions, and thus outside-in signalling, may also account for these effects.



**Figure 2.** Some of the signaling pathways regulated by integrin  $\alpha 6\beta 4$  in colorectal cancer cells. First is the cooperation between receptor tyrosine kinases (RTK), which via Src family of kinases (SFK) trigger phosphorylation of the cytoplasmic domain of  $\beta 4$  to activate the ERK and PI3K signaling pathways, which in turn regulate various cellular functions such as migration, proliferation and survival by the modulation of specific transcription factors (TFs) and activation of the Rho-GTPases. Second are the regulatory effects of the  $\alpha 6$  subunit on cell proliferation where  $\alpha 6A$  promotes the Wnt/ $\beta$ -catenin pathway and the expression of downstream effectors such as MYC while  $\alpha 6B$  appears to inhibit MYC activity by a possible interaction with the protein bridging integrator 1 (Bin1). MYC appears also as one key regulator of integrin expression since both *ITGB4* and *ITGA6* have MYC-responsive elements in their promoters as for *ESPR1* that encodes a splicing factor that regulate *ITGA6A* expression. Adapted from [18][36][39][40].

### 3. $\alpha 6$ Integrin Subunit (*ITGA6*) in CRC

### 3.1. Expression

As mentioned above, the integrin  $\alpha 6$  subunit is the only possible dimerization partner for  $\beta 4$ . *ITGA6*, as for *ITGA3* and *ITGA7* thought to have been derived from a common ancestor [20], is subject to alternative splicing of its exon 25, leading to the generation of two variants of the  $\alpha 6$  subunits,  $\alpha 6A$  and  $\alpha 6B$ , that are distinct in their unique cytoplasmic sequences [20]. Although the  $\alpha 6$  variants were reported and characterized more than 25 years ago and are likely to participate in distinct signalling cascades [41], the relationship between variant expression and distinctive cell functions has remained elusive especially in tumorigenesis [18].

As for many other epithelial cell types, intestinal cells can express both variants [41]. Closer analysis of  $\alpha 6A$  and  $\alpha 6B$  distribution in the intact normal human gut with a panel of anti- $\alpha 6$  antibodies revealed that  $\alpha 6A$  was predominantly detected in the proliferative cells of the small and large intestine while the  $\alpha 6B$  subunit was more restricted to the quiescent/differentiated cells lying on the villus and surface epithelium of the two intestinal segments [42][43]. Predominant expression of  $\alpha 6A$  in proliferative/undifferentiated cells and its gradual replacement by the  $\alpha 6B$  subunit in differentiating cells has also been confirmed in intestinal cell models [43].

Expression of the  $\alpha 6$  variants was investigated in CRC *in situ* and in adenocarcinoma cell lines. In CRC primary tumours, although most carcinoma cells expressing both  $\alpha 6A$  and  $\alpha 6B$  a clear loss of  $\alpha 6A/\alpha 6B$  segregation was observed [43]. Quantitatively, a clear increase in total *ITGA6* transcripts was noted in CRC as compared to the corresponding resection margins and this increase was attributed to an up-regulation in *ITGA6A* expression, with total levels of *ITGA6B* remaining comparable to those of the resection margins [44]. Consistently, all colorectal adenocarcinoma cell lines tested under proliferative conditions showed predominant *ITGA6A* expression.

### 3.2. Regulation of Expression

Information about transcriptional regulation of *ITGA6* expression is still limited. Among the consensus binding sites for the transcription factors SP1, NF- $\kappa$ B, AP1 and MYC identified on the *ITGA6* promoter [45], only SP1/SP3 have been confirmed [46]. Considering the fact that MYC expression is up-regulated in a large proportion of CRC [47][48] and that data indicating that MYC controls the expression of many genes in CRC cells including several key integrin subunits [40], which comprise *ITGB4* [25], MYC represents a potential regulator of *ITGA6* transcription. Pharmacological inhibition of MYC activity as well as molecular manipulations of intracellular MYC levels has shown a direct concordance between MYC levels and *ITGA6* expression in intestinal cells while chromatin immunoprecipitation assays have confirmed the functionality of the MYC binding site on the *ITGA6* promoter in the intestinal context [49].

Since neo *ITGA6* is expressed under the form of *ITGA6A* in CRC cells [24], the mechanism responsible for the up-regulation of this spliced form was further investigated. Alternative splicing of *ITGA6* has been relatively well studied and at least 10 splicing factors have been identified under various contexts but not in CRC cells. Among the various factors tested, the epithelial splicing regulatory protein 2 (ESPR2) was identified to be the main splicing factor responsible for *ITGA6A* expression in CRC cells [49]. It is noteworthy that ESPR1 was found to be responsible for *ITGA6* splicing in breast cancer cells [50] but in contrast to *ESPR2* that was found to be up-

regulated by MYC, *ESPR1* was not modulated in CRC cells by this factor [49]. Further identification of MYC as a direct activator of *ESPR2* active transcription indicates that MYC regulates both *ITGA6* and *ESPR2* expression resulting in the specific up regulation of *ITGA6A* in CRC cells [30].

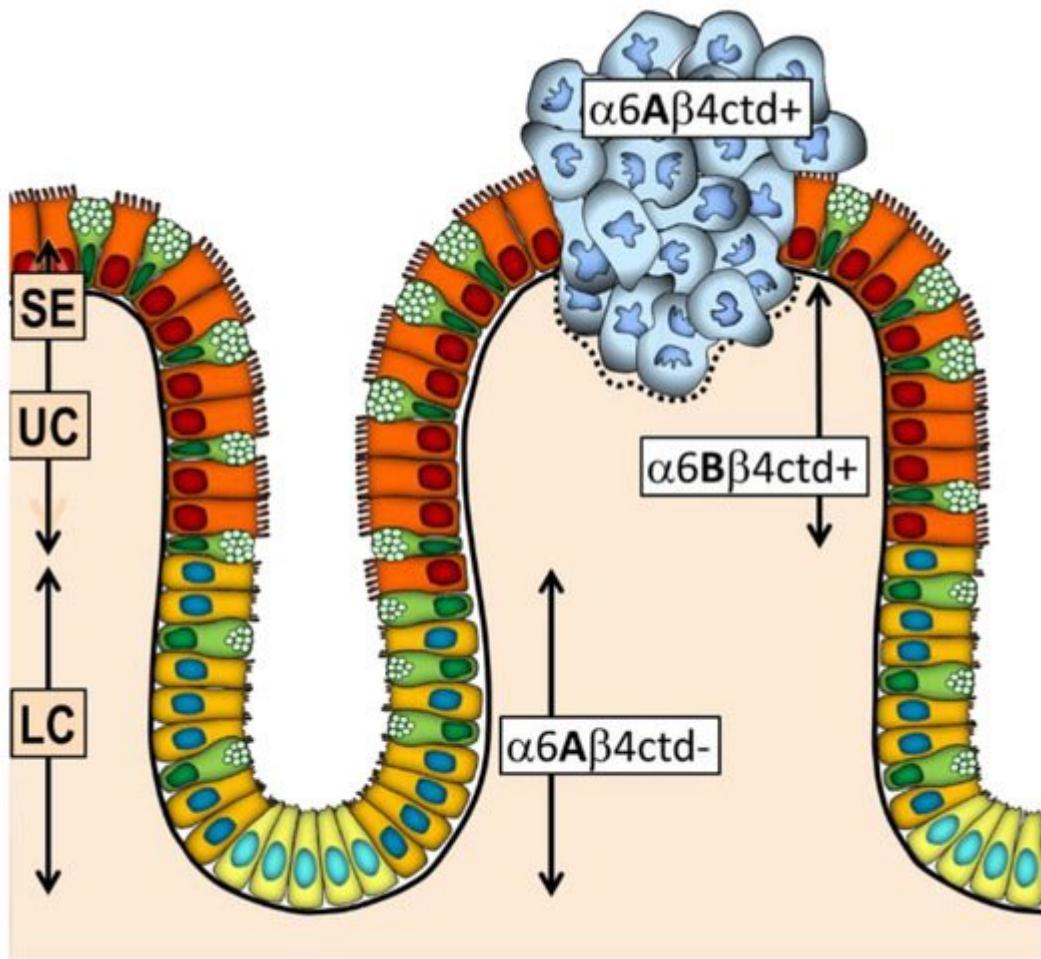
### 3.3. Change in Functionality

It is interesting to note that the cells of the crypt proliferative compartment, which predominantly express  $\alpha 6A/ITGA6A$  [42][43], are also the cells that express MYC in the normal colon [9]. Experimental studies using a normal intestinal epithelial crypt cell line showed that MYC regulates *ITGA6A* expression [49]. These data suggest that the MYC-dependent regulation of *ITGA6A* is a phenomenon occurring in the normal intestine, which appears to be exploited throughout the neoplastic process.

Indeed, colorectal cancer cell lines express 5–10 times more *ITGA6A* and MYC than their normal counterparts [49] while the integrin  $\alpha 6\beta 4$  was found to promote proliferation in colorectal cancer cells [44]. Specific knockdown expression of *ITGA6A* in various CRC cell lines was also accompanied by a reduction in the capacity of these cells to develop tumours [44]. Incidentally, the ability of  $\alpha 6\beta 4$  to promote proliferation in cancer cells was found to be mediated by activation of the Wnt/ $\beta$ -catenin pathway [44], a central signalling cascade required for intestinal crypt stem cell homoeostasis that is also exploited by CRC cells [51]. As MYC is a Wnt/B-catenin target gene [40], this suggests a feed forward loop for  $\alpha 6\beta 4$  and MYC expressions responsible for the overexpression of the two molecules in cancer cells. In this context, it is worth mentioning that experimental overexpression of  $\alpha 6B$  results in the inhibition of MYC activity [43], an effect potentially mediated by the selective interaction of the MYC inhibitor nucleoshaunting scaffold protein bridging integrator 1 with the  $\alpha 6B$  cytoplasmic domain [40].

## 4. The Integrin $\alpha 6\beta 4$ in CRC

In summary, while there is a clear segregation of  $\alpha 6\beta 4$  forms in the normal intestinal mucosa where  $\alpha 6A\beta 4$  is expressed by the proliferative cells of the lower crypt and  $\alpha 6B\beta 4$  is mainly expressed by the quiescent and differentiated cells of the upper crypt and surface epithelium, cancer cells predominantly overexpress  $\alpha 6\beta 4$  under the  $\alpha 6A\beta 4$  hybrid form (Figure 3), which appears to mediate both cell proliferation and suppression of anoikis [39][52].



**Figure 3.** Integrin  $\alpha 6\beta 4$  expressed in the human colonic mucosa. In the lower crypt (LC), which contains stem cells (yellow) and proliferative absorptive and goblet cell precursors (gold and light green),  $\alpha 6\beta 4$  is expressed under the form of  $\alpha 6A\beta 4ctd-$  while in the upper crypt (UC) and surface epithelium (SE), which contains quiescent absorptive and goblet cells (orange and green), it is under the form of  $\alpha 6B\beta 4ctd+$ . In carcinoma (blue), this segregation is lost and  $\alpha 6\beta 4$  is predominantly expressed under the pro-proliferative form  $\alpha 6A\beta 4ctd+$ .

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