Discussion on Wnt Pathway activity in metastasis

APC truncated mutations

The size of the truncated protein has an influence on the numbers of polyps. For example the APC^{min} mutant in which the *apc* gene harbours an additional stop codon at codon 850 results in high amounts of polyps (~120) in the intestine [1] while a truncation at codon 716 (APC^{716}) can give rise even to more than 300 polyps in the small intestine [2]. On the contrary, a longer truncated APC isoform, truncated at stop codon 1638, of APC^{1638N} may only give rise to 3 polyps [3] indicating that a larger truncated form of APC still harbours an inhibitory activity due to the β-catenin inhibitory domain (CID) which is located in the mutation cluster region (MCR) and can thus be found in many truncated APC's found in human tumours [4,5]. These truncated forms still contain sufficient amino acid repeats to phosphorylate β-catenin followed by degradation by the destruction complex [5,6]. Furthermore, it has been described that tumours with APC LoF mutations do require canonical wnt ligands in order to have activated Wnt pathway activity [7,8]. Compared to wild type APC, the phosphorylation of β-catenin capacity seems to be relatively weak but highly active, thus still having significant impact on the regulation of β-catenin in cancer cells [6]. It has been demonstrated that silencing of truncated APC leads to increased β-catenin-mediated transcriptional activity and β-catenin protein level [9] which is in accordance that truncated APC can phosphorylate β-catenin for degradation.

As for mutation of β-catenin, it occurs even less frequently than mutations of both APC alleles [10] and it has been shown that in Wilms tumours, mutational-activated β-catenin induces transcription of mainly genes involved in proliferation or genes that code for proteins involved in the inhibition of the Wnt pathway [11]. To conclude, in our modelling framework, we can only account for full inhibition or activation of genes. More refined modelling might be needed to account for these forms of truncated APC and mutations.

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