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P15. A genetic mouse model to identify the role of the immune adapter protein MyD88 in colorectal cancer

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Background

Pattern recognition receptors from the Toll-like receptor (TLR) family are pivotal components of innate immunity, and have been shown to contribute to colon cancer formation. However, the molecular and cellular mechanisms underlying TLR-signaling in colon cancer remain unclear. The adapter protein *Myeloid-differentiation factor 88* (MyD88) is shared between several TLRs and the Interleukin-1 receptor family. MyD88-deficiency protects mice from intestinal cancer formation in genetic models for colon cancer. The genetic mouse model presented here allows tissue-specific expression of MyD88, and thereby the dissection of the complex interaction between tumour and immune system during intestinal carcinogenesis.

Material and methods

Insertion of an 'intron-gene-trap' flanked with loxP motifs into the first intron of the MyD88 gene locus leads to global inactivation of *myD88* expression ($MyD88^{LSL}$), faithfully phenotyping a global gene knockout. Tissue-specific re-expression of MyD88 in mice is mediated based on the Cre-recombinase. Breeding of $MyD88^{LSL}$ mice with LysMCre or pvillin-Cre mice leads to tissue-specific excision of the 'intron-gene-trap', retaining endogenous regulation of gene expression. MyD88 expression and successful reconstitution of TLR-signaling was detected in either myeloid cells ($MyD88^{MYEL}$) or intestinal epithelial cells ($MyD88^{IEC}$). Subsequently, these animals were mated with $Apc^{1638N/+}$ mice, an established genetic mouse model for human colon cancer.

Results

Global MyD88 deficiency dramatically decreased tumour incidence and aggressiveness in $Apc^{1638N/+}$ mice. Re-expression of MyD88 in intestinal epithelial cells only partially restored tumor formation. On the other hand, reconstitution of MyD88 expression in myeloid cells triggered tumour development virtually indistinguishable from parental $Apc^{1638N/+}$ mice. Activation of the canonical Wnt signaling pathway, induced by loss of function of Apc, was independent of MyD88. In contrast, MyD88 expression was required for full activation of MAPK/ERK signaling in intestinal epithelial cells. Furthermore, our results suggest a pro-tumorigenic function for the pro-inflammatory cytokines IL-1beta and IL-6, which were produced in a MyD88-dependent fashion by myeloid cells.

Conclusions

MyD88-mediated signaling has pro-tumorigenic effects in both IECs and in myeloid cells, but via different mechanisms. Moreover, MyD88 function in myeloid cells is crucial for intestinal tumour development, and its inhibition may form a promising therapeutic strategy.

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