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The immune response to sporadic colorectal cancer in a novel mouse model.

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Source

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Abstract

Current mouse models do not reflect the sporadic nature of colon cancer and do not allow the analysis of antitumor immune response because of the lack of known tumor-specific antigens. Two transgenic mouse models with spontaneous tumor development were generated, directing the expression of SV40T antigen (Tag) either constitutively (Vil-Cre × LoxP-Tag-transgenic mice) or stochastically (Vil-Cre-ER(T2) × LoxP-Tag-transgenic mice) into the putative stem cell region of the crypt of Lieberkühn. Tumor development and antitumor immune response were monitored. Vil-Cre × LoxP-Tag mice developed multiple adenocarcinomas of the small intestine and colon at an average age of 6 months. During the tumor development, Tag-specific immunoglobulin G (IgG) antibodies were induced in half of the mice, although they had developed neonatal cytotoxic T lymphocyte (CTL) tolerance. This model shows similarity to hereditary colon cancer but not to the sporadic tumor development. Therefore, the conditional Vil-Cre-ER(T2) × LoxP-Tag mice were established, in which expression of the dormant Tag was induced by stochastic, tissue-specific activation of Cre recombinase. These mice spontaneously developed highly invasive, metastasizing colon carcinomas at an average age of 20 months. Colon carcinomas expressed epithelial and/or neuroendocrine markers depending on the grade of differentiation. Young Vil-Cre-ER(T2) × LoxP-Tag mice had retained CTL responses against epitope IV of Tag. The tumors induced strong anti-Tag IgG responses. We report, for the first time, a mouse model based on stochastic, tissue-specific activation of a dormant oncogene in the colon allowing the analysis of antitumor immune response against primary colorectal cancer.

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