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A new gene therapy: Gene delivery of anti-cathepsin L single-chain variable fragment by lentiviral vector inhibits tumor progression induced by human melanoma cells

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We previously demonstrated that the switch from non-to highly tumorigenic phenotype of human melanoma cells is directly related to procathepsin L secretion, which increased cell resistance to complement-mediated cell lysis and immune system. Involvement of procathepsin L secretion in tumor growth was clearly demonstrated by three different strategies: (1) inhibition of secreted procathepsin L activity; (2) increase of procathepsin L secretion; and (3) inhibition of procathepsin L secretion. This latter strategy was triggered by intracellular expression of anti-human cathepsin L single-chain variable fragment (ScFv). These previous experiments were performed by processing melanoma cells before their injection into nude mice. We herein designed a new lentiviral vector in which this anti-cathepsin L ScFv was cloned. This lentiviral vector was optimized to allow the highest intracellular expression of anti-cathepsin L ScFv in transduced melanoma cells. In these transduced cells, procathepsin L secretion was strongly inhibited. In addition, injection of this anti-cathepsin L ScFv lentiviral vector into tumors already induced in nude mice inhibited tumor growth and associated angiogenesis. This is the first report to demonstrate that targeting procathepsin L secretion with anti-cathepsin L ScFv lentiviral construct constitutes a new gene therapy in the challenge to inhibit the growth of tumors induced by human melanoma cells. In addition, we demonstrated in human melanoma cells that procathepsin L secretion is regulated by down regulation of Rab4A expression. Rab4A regulation by modifying procathepsin L secretion, switches the tumorigenic phenotype of human melanoma cells in nude mice. Rab4A constitutes as a new target for gene therapy.

Biography

Raymond Frade, PhD in Biochemistry, was recruited at 22 as the youngest assistant-professor of the University Pierre et Marie Curie in Paris. He was promoted associate-professor, then full professor in Biochemistry. After, he was recruited as Director of Research at the INSERM (the French NIH). He managed successively three INSERM Units (U.23, U.354 and U.672), during 22 years, in Paris area. He published more than 81 papers in reputed journals with high impact factors. Its main contributions are: isolation and characterization of the Epstein-Barr virus receptor, discovery of the new human gene RB18A/MED1 and the new gene therapy to inhibit tumor progression induced by human melanomas.

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