Use of engineered mesenchymal stem cells against cancers

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Abstract

Gene-directed enzyme pro-drug therapy (GDEPT) consists in expression of a suicide gene in tumor cells allowing *in situ* conversion of the pro-drug into cytotoxic metabolites. In previous work, we demonstrated that the combination of a mutant CYP2B6 with NADPH cytochrome P450 reductase (CYP2B6TM-RED), as a suicide gene, and cyclophosphamide (CPA) might constitute a powerful treatment for solid tumors. The efficiency of this combination was mainly due to i) an optimized suicide gene able to metabolize efficiently CPA ii) an efficient bystander effect, iii) the development of an antitumor immune response. Major impediments were the targeting of the suicide gene specifically to the tumor cells and its low expression into tumor cells. Recently, therapies based on genetically engineered mesenchymal stem cells (MSCs) expressing suicide gene have received a great deal of attention because of their therapeutic potential to treat solid tumors. Indeed, MSCs possess an extraordinary ability to home into tumors due to the inflammatory mediators which are found at the site of a tumor. MSCs can be easily isolated, from tissues such as bone marrow (BM-MSCs) and adipose tissue (ACS), expanded in culture and efficiently transduced with recombinant viral vectors leading to important and stable expression of the suicide gene. Once the transduction is performed, the most efficient clone for bioactivation of the prodrug can be selected and used for several patients. Indeed, given the minimal expression of the major histocompatibility complex MHC-I and MHC-II, allogeneic expanded adipose-derived stem cells (eASC) delivered locally are well-tolerated and currently in clinical Phase III clinical trials for the treatment of inflammatory and auto-immune diseases. Murine MSCs were genetically engineered *ex-vivo* to stably express luciferase or CYP2B6TM-RED. The most efficient clones were selected. MSCs expressing luciferase were used to follow the future of MSCs after their intratumoral injections in animal models. MSCs expressing CYP2B6TM-RED were used to check *ex vivo* and *in vivo* their efficiency to bioactivate CPA and destroy neighboring tumor cells through a by-stander effect. Intratumoral injections of CYP2B6TM-RED-MSCs and CPA allowed a complete eradication of the tumor in 33% of the mice without any recurrence four months later. Different experiments

Biography

Waziers I completed her PhD in Molecular Pharmacology, Experimental Pharmacology and Metabolism, Physiology of Nutrition. She is the member of administration council of the Faculty of Medicine in Paris Descartes University, member of the American Association for Cancer Research. She has been appointed as the Mayor of Lignières en Vimeu from 1995, President of the Community of Communes of the Region of Oisemont from 2014, Departmental Councilor from 2014. Her special research areas are xenobiotic metabolism, toxicology, molecular biology, cancer, resistance to chemotherapy, gene therapy, transcriptomic, metabonomic.