Development of new immunotherapies against melanoma based on the use of Salmonella carrying plasmids encoding for IL18

Amy Mónaco¹, Magdalena Vola¹,², Gabriela Kramer¹, Lucía Yim¹, Rodrigo González¹, Caroline Agorio³, Alejandro Chabalgoity¹, María Moreno¹

¹Depto. de Desarrollo Biotecnológico, Instituto de Higiene, ²Depto. Bacteriología y Virología, Instituto de Higiene, ³Catedra de Dermatología, Hospital de Clínicas

Skin cancer in its different types constitutes the most common cancer, being melanoma one of the most aggressive solid tumors with a poor response to standard treatments. Because of its immunogenicity, immunotherapy is an attractive strategy to address it. Those treatments based on the use of live attenuated Salmonella carrying a plasmid encoding for IL18 are promising, since preliminary results showed longer survival when administered orally to bearing tumor mice. In this work, we designed different plasmid constructs carrying IL18 under eukaryotic or prokaryotic promoters, constitutive or inducible, and with or without secretion sequence. Subsequently we evaluated its antitumor activity in three models of melanoma: 1) classic melanoma model, injecting B16F1 cells subcutaneously (sc), 2) second tumor challenge with B16F1 sc and 3) model of minimal residual disease (MRD) with B16F10 intradermally (id). So far we have constructed two strains of S. typhimurium SL3261 and LVR01 carrying IL18 under constitutive eukaryotic promoter (VR1012), and a strain carrying IL18 under inducible prokaryotic promoter (pLVR21), which were evaluated intratumorally in the classic model. Preliminary results showed that both strains carrying VR1012 plasmid behave similarly, slowing tumor growth in comparison to the control group. Furthermore, LVR01 carrying pLVR21 has proved to be the best therapy up to now, significantly reducing tumor growth and prolonging mice survival over a third compared to the control. The fact that its induction is mediated by hypoxia is essential since tumor microenvironment is poorly aerobic.

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