Targeting serine/glycine metabolism to improve radiotherapy responses in Non-Small Cell Lung Cancer

A. Sánchez-Castillo[1], E. Heylen[2], J. Hounjet[1], N.G. Lieuwes[3], R. Biemens[3], L. Dubois[3], K. Reynders[1,4], K. Rouschop[1], R.D.W. Vaes[1], K. De Keersmaecker[2], M. Lambrecht[5], L.E.L. Hendriks[6], D.K.M. De Ruysscher[1], M. Vooijs[1], K.R. Kampen[1,2]

[1] Maastricht University Medical Center+, Department of Radiation Oncology (MAASTRO), GROW School for Oncology and Reproduction, Maastricht, The Netherlands; [2] Laboratory for Disease Mechanisms in Cancer, Department of Oncology, KU Leuven and Leuven Cancer Institute (LKI), Herestraat 49, 3000 Leuven, Belgium; [3] Maastricht University Medical Center+, Department of Precision Medicine, GROW School for Oncology and Reproduction, Maastricht, The Netherlands; [4] Experimental Radiation Oncology, Department of Oncology, KU Leuven and Leuven Cancer Institute (LKI), Herestraat 49, 3000 Leuven, Belgium; [5] Department of Radiation Oncology, University Hospital Leuven, Leuven, Belgium; [6] Maastricht University Medical Center, Department of Pulmonology, GROW School for Oncology and Reproduction, Maastricht, The Netherlands.

Abstract

Lung cancer is the second most common cancer and about 85% of lung cancers are classified as non-small cell lung cancer (NSCLC). The current NSCLC therapeutic options reach overall survival rates of ~50%, but most tumors eventually develop treatment resistance. Recently, there has been a growing interest in the activation of de novo serine/glycine (ser/gly) synthesis, which branches from the glycolysis, and its association with treatment resistance. Yet, ser/gly metabolic rewiring in response to radiotherapy (RT) remains unknown. We hypothesized that ser/gly metabolism supplies ATP, nucleotides, and antioxidants to support the survival of cancer cells upon RT. Therefore, targeting novo ser/gly synthesis with the SHMT inhibitor sertraline may re-sensitize cancer cells to RT.

Metabolomics mass spectrometry analysis revealed a decrease in serine and glycine in NSCLC cell lines and a decrease of ser/gly synthesis-downstream metabolites, i.e., homocysteine, threonine, and GSH in the blood plasma of NSCLC patients in response to RT. These results suggest that cancer cells use serine, glycine, and downstream products to survive RT. Consequently, the combination of sertraline and RT impaired the growth of NSCLC cells and reduced their clonogenic capacity. This could be dedicated to a significant increase in mitochondrial reactive oxygen species (ROS). In mice bearing subcutaneous lung tumors we could validate a significant reduction in tumor growth only in the group receiving sertraline together with RT. In addition, the combination treatment could remodel the immune landscape of the tumors by increasing the recruitment of immune cells by generating increased levels of IFN-γ. This improved immune landscape (reduced IL-4, induced myeloperoxidase, IFN-γ and CD11b), associated with reduced glycine/threonine and an accumulation of homocysteine blood serum levels, as homocysteine requires glycine to form the antioxidant GSH. In our NSCLC patients' blood plasma samples, threonine/betaine metabolites related to IL-4 blood levels, and homocysteine was linked to reduced G-CSF blood levels. In addition, as in our animal model, we observe a strong correlation between IFNγ and CD11b immune cells. These data support that tumor derived serine/glycine metabolism can modulate the immune landscape. In conclusion, our findings highlight that targeting serine/glycine metabolism can overcome RT resistance and improve therapeutic outcomes in NSCLC.