

Lipopolysaccharides induce survival in lung cell lines – The role of protein-kinases activation

Mira Yasemin Gökyildirim¹, Florentine Subtil², Ulrich Grandel¹, Gabriele Dahlem¹, Florian Leinberger², Rita Engenhardt-Cabillic², Werner Seeger³, Ulf Sibelius¹, Friedrich Grimminger¹, Katja Hattar¹

¹Medical Clinic IV/V, Department of Internal Medicine, UGMLC, University of Giessen

²Clinic for Radiotherapy and Radiooncology, UGMLC, Philipps-University Marburg

³Medical Clinic II, Department of Internal Medicine, UGMLC, University of Giessen

Purpose: Pulmonary infections are common complications in patients with lung diseases and worsen prognosis. These patients often show a worse approach to treatments. Common pathogens found in patients are gram-negative bacteria. Their virulence is caused by Lipopolysaccharides (LPS). LPS is known to activate multiple pathways in pulmonary epithelial cells. This could induce an increased survival and proliferation in human lung cell lines.

Methods: Radiation was used to kill cells. Colony formation assays were performed to show an increased proliferation and survival after LPS treatment and radiation. Cells were treated with different doses of LPS (0, 0,1, 1 and 10 µg/ml) and exposed to ionizing radiation (0, 1, 2, 4, 6 and 8 Gy). A defined number of treated cells were plated on dishes and after 10 days the colonies were counted. The plating efficiency and the survival rate were calculated.

In parallel, proteins were isolated and proteome arrays were performed. With this proteome array potential target proteins were found. Up-regulated target proteins were inhibited in LPS-treated cells before irradiation.

Results: Ionizing radiation induced a reduction in survival. LPS promotes an increased survival in the lung cell line. This effect was dose dependent and most pronounced when 10 µg/ml LPS was used. The Proteome Array shows an upregulation of the cAMP response element-binding protein (CREB) and EGFR (Epidermal Growth Factor Receptor) after LPS treatment and radiation. Also the Src family members Fyn, Lyn and Fgr were upregulated after LPS treatment and radiation. After CREB binding protein (CBP) or EGFR inhibition the LPS-induced survival was decreased.

Conclusion: The LPS treatment leads to an increased survival and proliferation after radiation. An inhibition of possible target proteins like CREB or EGFR may serve as a potential treatment to overcome this increased survival and proliferation after pulmonary infections.