A possible role for the intracellular Ca2+-homeostasis in the development of cisplatin-resistance in squamous lung carcinoma cells

Huber, Rudolf M.; Oelmez, Hamza; Bergner, Albrecht

Pneumology, Medizinische Klinik-Innenstadt, LMU, Munich, Germany

Background: In the treatment of lung cancer, the effectiveness of chemotherapy is hampered by the development of therapy-resistance. Calcium is a universal second messenger involved in the regulation of virtually all cell function including apoptosis and cell death. Aim of this study was to investigate if the intracellular Ca2+-homeostasis of lung cancer cells may influence the development of therapy-resistance to cisplatin.

Methods: ATP served as an agonist to stimulate squamous lung carcinoma cells (EPLC) and the increase in cytoplasmatic calcium ([Ca2+]c) was quantified using fluorescence microscopy. The Ca2+-indicator rhod-2 was used to quantify the mitochondrial Ca2+-content. EPLC cells were exposed to 0.5, 1 and 2 µg/ml cisplatin for 3h simulating the in vivo pharmacokinetics. The Ca2+-chelator BAPTA was used to study the effects of a reduced [Ca2+]c on the effectiveness of cisplatin.

Results: Using appropriate inhibitors, we could show that the ATP-induced Ca2+-increase was due to Ca2+-release from the sarcoplasmic reticulum involving IP3- and Ryanodine-receptors with Ca2+-influx from the extracellular space playing a minor role. Exposure to cisplatin led to a time dependent increase in the mitochondrial Ca2+-content. After 4 “cycles” of cisplatin the EPLC cells showed an increased survival compared to naïve EPLC cells. This therapy-resistance could be mimicked buffering [Ca2+]c with BAPTA. In the resistant clone, the ATP-induced Ca2+-increase was found to be significantly reduced compared to naïve cells.

Conclusions: The intracellular Ca2+-homeostasis of lung carcinoma cells plays a significant role in the development of cisplatin-resistance and may therefore constitute a novel approach to overcome therapy-resistance.

Supported by the Deutsche Forschungsgemeinschaft and the Deutsche Gesellschaft für Pneumologie und Beatmungsmedizin.

A6-05 Cancer Genetics and Tumor Biology, Mon, 13:45 - 15:30

Clinicopathologic Implications of minimal genomic alteration regions (MAR) identified in non-small cell lung cancer by using whole genome array-CGH

Kim, Tae-Min1 Shin, Seung-Hun1 Kwon, Mi-Seon2 Xu, Hae-Dong1 Kim, Mi-Young1 Jung, Seung-Hyun1 Choi, Hye-Sun1 Jeong, Yong-Bok1 Park, Jae-Kil1 Chung, Yeun-Jun1

1 Department of Microbiology, Catholic University of Korea, Seoul, Korea 2 Department of Pathology, Dankook University Medical College, Cheonan, Korea 3 Department of Thoracic Cardiovascular Surgery, St Mary’s Hospital, Catholic University of Korea, Seoul, Korea

Background: Lung cancer is the most common incident form of malignancy and also the leading cause of cancer death worldwide. Although many genomic alterations have been observed in lung cancer, their clinicopathological significance has not been thoroughly investigated. This study screened the genomic aberrations across the whole genome of non-small cell lung cancer cells with high-resolution and investigated their clinicopathological implications.

Method: One Mb-resolution array comparative genomic hybridization (array-CGH) was applied to 31 squamous cell carcinomas and 24 adenocarcinomas of lung. Copy number alteration was detected by using web based array-CGH analysis software named arrayCyCGH (http://genomics.catholic.ac.kr/arrayCGH/). The recurrent genomic alterations were analyzed for the association with the clinicopathological features of lung cancer. Significance of the association between MAR and