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The role of estrogen receptor alpha in lung cancer development and growth, a novel therapeutic target

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Lung cancer is the leading cause of cancer death. The treatment is very limited for the advantaged lung cancer and this is partly due to our poor understanding of lung carcinogenesis and the lack of effective treatment targets. Estrogen receptor alpha (ERa) plays a role in lung biology and pathology. Smoking carcinogen N-nitrosamines such as NNK is catalyzed by cytochrome P450 (CYP) family before they can promote lung cancer development and growth. However, the association between both ERa and CYP is unknown in smoking-induced lung tumorigenesis. In this study, CYP1B1, ERa and ERb were analyzed in the lung tumor mouse model and human lung cancer tissues and their roles in lung tumor development and growth were explored using various cellular and molecular approaches. Our *in vivo* study demonstrated that CYP1B1, ERa and ERb were over-expressed at the early stage of NNK-induced lung tumorigenesis. Microarray analysis found that ERa was involved in the ERK/MAPK Pathway. NNK activated RAS/ERK/AP1 as it remarkably increased the levels of p-ERK, c-Fos and c-Jun, but inhibited multiple negative regulators of Ras/ERK/AP1, pdcd4, spry1, spry2 and Btg2 through up-regulating miR-21. Both CYP1B1 siRNA and ERK specific inhibitor suppressed NNK-mediated ERb up-regulation, suggesting that ERa is down-stream of CYP1B1and ERK. ERK inactivation led to the accumulation of CYP1B1, indicating that CYP1B1 is up-stream of ERK activation. Inhibition of ERK or ERa decreased NNK-induced cell proliferation, and block of CYP1B1 or ERa induced apoptosis in lung cancer cells. Therefore, we can conclude that ERa up-regulated by smoking carcinogen NNK contributes to the lung carcinogenesis. NNK-mediated ERa induction is via CYP1B1 and ERK activation. The inhibition of CYP1B1 or ERa may arrest the lung cancer cell proliferation and growth, indicating that they are likely to be novel therapeutic targets against smoking-related lung cancer.

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Current algorithm for treatment of advanced NSCLC patients: How to include active immunotherapy

Gisela Gonzalez

This lecture will address how active immunotherapy could be included in the current algorithm for treatment of advanced NSCLC patients. Despite the availability of different treatments for advanced NSCLC, all of them have a palliative intention and a cure for the disease is unlikely. Advanced lung cancer remains thus as an unmet medical need. Chemotherapy has been used as the therapy of choice for advanced NSCLC patients, but has mainly limited by the patient´s performance status. More recently, targeted therapies have introduced more specific treatment options that show efficacy in specific niche of patients, but usually provoke early resistance; most of the best drugs currently used for treatment of advanced NSCLC show small increases in patient survival with severe associated toxicity. Novel drugs with low toxicity that could be given chronically to control the advanced disease can make a difference. Active-specific immunotherapy is an area of oncology that is rapidly expanding with encouraging results. Cancer vaccines have shown to increase NSCLC patient survival in clinical trials. Safety of cancer vaccines suppose a new hope for cancer therapy, and this unique characteristic makes possible its use in sub-sets of patients that cannot receive other approved treatments because their high toxicity.

Biography

Gisela Gonzalez has worked as Full Development Team Leader of novel immunotherapeutic approaches for cancer therapy 25+ years, during which time she has authored 30+ peer-reviewed papers as well as patents based in 5 invention objects granted in 30+ countries. She has received two awards from the National Academy of Sciences from Havana, Cuba and a special award granted by the Cuban Ministry of Science and Technology because of the impact of her scientific results in human health.