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ACETYLATION OF SRPK1 BY TIP60 MODULATES ALTERNATIVE SPLICING IN CISPLATIN-RESISTANT BREAST CANCER CELLS

Chemotherapy is an important treatment option for breast cancer in adjuvant and neoadjuvant settings. But its clinical utility is severely compromised by drug resistance acquired by the cancer cells. Many genes involved in regulating drug responsiveness are subjected to pre-mRNA alternative splicing and serine-arginine protein kinase 1 (SRPK1) has been established as a critical regulator of splicing; however, it remains unknown whether the chemodrug cisplatin affects the expression and function of SRPK1 to cause drug resistance. In this study, we found that cisplatin induced SRPK1 acetylation in a Tip60-dependent manner in breast cancer cells. Surprisingly, in the corresponding cisplatin-resistant cells, the drug decreased SRPK1 acetylation and increased its phosphorylation, resulting in three critical molecular events: (i) shift of SRPK1 to the nucleus, (ii) elevated phosphorylation of serine/arginine-rich splicing factors (SRSFs), and (iii) alternative splicing of some key regulators of apoptotic signaling, such as BCL2L1 and MCL-1, towards the production of anti-apoptotic isoforms. Significantly, we were able to resensitize the cisplatin-resistant cells by enhancing Tip60-dependent acetylation of SRPK1 or blocking its kinase activity with a specific inhibitor of SRPK1, SRPIN340. Hence, our study reveals a key role of SRPK1 in the development of cisplatin resistance in breast cancer cells and suggests a potential therapeutic avenue for overcoming such drug resistance.

Friday
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3.00 PM – 4.00 PM
Seminar Room, MD10
Level 2, Anatomy Museum

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