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Negative regulators of cell death signalling pathways in cancer

Cancer is a primary cause of human death with a global economic toll of around US$1.4 trillion each year. It is estimated that about 12 million people will yearly die of cancer by 2030. Conventional cancer therapies such as chemotherapy or radiotherapy usually interrupt vital cellular events and are often associated with side-effects, tumour drug-resistance, and cancer recurrence. The main challenge in conventional therapies is that cancerous tissues evolve drug-resistance rapidly through inhibition of cell death signalling pathways such as apoptosis, ferroptosis, necroptosis, autophagy, and anoikis.

De-regulation of cell death principally occurs through the activation of negative regulators suppressing cell death mechanisms during oncogenesis. For instance, resistance to apoptosis is known as the hallmark of cancer leading to tumorigenesis and the development of drug-resistance. Therefore, to overcome cancer drug-resistance, it is important to deactivate the negative regulators of cell death pathways.

We critically discussed the current state of knowledge on targeting negative regulators of cell death pathways and evaluated the advances in clinical and pre-clinical research on biomarkers of negative regulators. It aimed to provide a comprehensive platform for designing effective combinational therapies including novel agents for reactivating cell death signalling pathways or targeting alternative resistance pathways to increase the chances for anti-tumour responses. In conclusion, understanding negative regulators of signalling pathways will help to identify potential therapeutic targets, and design diagnostic and prognostic biomarkers. Strategically “molecularly targeted therapies” are emerging through investigation of apoptotic signalling pathways. However, evidence is accumulating that non-apoptotic modes of cell death such as necroptosis and autophagy also play a significant role in inducing drug-resistance, necessitating more attention for drug discovery.

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