Time to die (or not): The role of a molecular timer in regulation of apoptosis signalling

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Apoptosis execution is a key process of programmed cell death that has critical roles in the innate prevention of cancer and in response to cancer treatment. A crucial component of this pathway is the apoptosome, a platform for the recruitment, activation and cleavage of the key apoptosis regulator pro-caspase 9 (PC9). Recent findings have shown that autocatalytic processing of PC9 to C9(p35/p12) on the apoptosome temporally shuts down apoptosome activity due to the low affinity of the processed form C9(p35/p12) to the apoptosome, forming a molecular timer. However, it is unknown what contribution, if any, this has on apoptosis execution in real cellular scenarios and its relative importance compared to the major inhibitor of apoptosis XIAP. In order to broadly analyse and delineate the combined contributions of XIAP and the apoptosome molecular timer to apoptosis execution we utilised a systems biological modelling approach. We screened physiologically relevant concentration ranges of critical proteins for cellular scenarios where the molecular timer can actively prevent apoptosis. We discovered that the molecular timer can prevent apoptosis execution in specific scenarios after complete or partial initiation of apoptosis signalling. Furthermore, its ability to prevent apoptosis is intricately tied to a synergistic combination with XIAP. Finally, we demonstrate that our model of apoptosis execution is prognostic for survival in a cohort of patients with stage III colorectal cancer and that the molecular timer contributes to patient apoptosis resistance. We postulate that the physiological function of the molecular timer is to aid XIAP in the shutdown of apoptosis signalling in the event of failed apoptosis execution. This shutdown potentially facilitates a switch to pro-inflammatory responses that are actively inhibited by apoptosis signalling.