TCOF1 AS A NOVEL NUCLEOLAR CASPASE-2 SUBSTRATE: A TALE OF TWO (OR THREE) CASPASES

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Background: Caspase-2 is a member of the caspase family of proteases that serve critical roles in cell death and inflammation. Caspase-2 is unique among caspases as it has been identified as a tumor suppressor in various tissue types. However, the mechanism of how caspase-2 suppresses tumors remains unclear, as it serves multiple independent functions in DNA damage induced apoptosis and cell cycle control. As a protease, caspase-2 executes its functions by cleavage of specific target substrates. By studying the substrates of caspase-2, how it can perform multiple roles to promote tumor suppression may become clearer. Our lab discovered that caspase-2 is activated preferentially in the nucleolus in response to DNA damage. We hypothesize that caspase-2 targets nucleolar substrates in response to DNA damage to mediate either apoptosis or cell cycle arrest. By searching proteomics data, we uncovered the Treacher Collins Syndrome Protein (Treacle/TCOF) as a potentially overlooked nucleolar substrate of caspase-2. TCOF has been reported to interact with NSB1 to mediate the shutdown of ribosomal gene transcription in response to DNA damage.

Materials/Methods: To investigate TCOF as a caspase substrate, we used in vitro transcription and translation with radioactive methionine to label TCOF1 and incubated it with recombinant human caspases. We used confocal microscopy to visualize TCOF in vitro.

Results: Our data suggests that in the absence of caspase-2, TCOF mislocalizes from the nucleolus, which could inhibit this reported function. Further, we show that while TCOF is a caspase-2 substrate in a cell free system, it is also readily cleaved by other caspases, making it difficult to ascertain which caspases are contributing to its cleavage in vitro, even though other caspases are not typically found in the nucleolus.

Conclusions: Discovering how caspase-2 influences the role of TCOF, and indeed, which other caspases could be involved in this function are important for understanding not only the tumor suppressor function of caspase-2, but also how other caspases could be serving undiscovered functions in the nucleolar compartment.

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