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REVIEW ARTICLE

Is there something else besides the proapoptotic AVPI-segment in the Smac/DIABLO protein?

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Abstract In mammals, apoptosis is the main mechanism to eliminate unwanted cells, securing tissue homeostasis and consequently maintaining the health in the organism. Classically, apoptosis culminates with the activation of caspases, which are enzymes that display cysteine protease activity to degrade specific substrates implied in essential cellular processes. This process is highly regulated. A key regulation mechanism is mediated by the Inhibitor of Apoptosis Proteins (IAPs) family members, which inhibit the activated forms of caspases through physical interaction with them. Smac/DIABLO, a mitochondrial protein that is translocated to the cytoplasm in apoptotic conditions, derepresses the IAP-mediated caspase inhibition through physical interaction with IAPs. The first four amino acids (AVPI) of Smac/DIABLO mediate the interaction with IAPs and subsequent apoptosis induction. This interaction has lead to the creation of small molecules mimicking the AVPI segment for potential anticancer therapy. Nevertheless, several studies have pointed out the existence of AVPI-independent functions of Smac/DIABLO. The aim of this review was to provide a landscape of these underestimated AVPI-independent biological functions that have been observed using different approaches, such as the study of endogenous splice variant isoforms and truncated and mutated artificial proteins.

PALABRAS CLAVE
Smac;
DIABLO;

¿Existe algo adicional al segmento pro-apoptótico AVPI de la proteína Smac/DIABLO?

Resumen La apoptosis es uno de los principales mecanismos en los mamíferos para eliminar células no deseadas, asegurando la homeostasis de los tejidos y, consecuentemente, la salud

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de los mismos. De forma clásica, la apoptosis finaliza con la activación de las caspasas, enzimas que despliegan actividad de proteasas de cisteína, involucradas en la degradación de sustratos específicos implicados en procesos celulares esenciales. El proceso apoptótico se encuentra altamente regulado. Un mecanismo de regulación es el mediado por los miembros de la familia de las Proteínas Inhibidoras de la Apoptosis (PIA), las cuales inhiben a las formas activas de las caspasas a través de la interacción física con estas. Smac/DIABLO, proteína mitocondrial que es translocada al citoplasma en condiciones apoptóticas, antagoniza la inhibición de las caspasas mediante su interacción física con las PIA. Los cuatro primeros aminoácidos (AVPI) de Smac/DIABLO intervienen en su asociación con las PIA y la subsecuente inducción apoptótica. Esto ha guiado a la generación de pequeñas moléculas miméticas del segmento AVPI para el uso potencial como una terapia anti-cancerígena. Sin embargo, varios estudios han indicado la presencia de funciones en Smac/DIABLO independientes del AVPI. El objetivo de esta revisión fue proporcionar un panorama de estas funciones biológicas desestimadas —independientes al AVPI— las cuales se han observado utilizando diferentes aproximaciones, como el estudio de las isoformas generadas por el procesamiento alternativo del gen y la síntesis de proteínas artificialmente mutadas.

1. Apoptosis

Apoptosis, or programmed cell death, is a natural mechanism that secures tissue homeostasis through the elimination of both damaged and unwanted cells. The apoptotic program culminates with the degradation of specific proteins implied in key cellular processes by a group of enzymes termed caspases. Caspases are expressed as zymogens, the inactive configuration of their cysteine protease activity. These enzymes are divided into two groups: initiator caspases (caspase-2, -8, -9 and -10) and effector caspases (caspase-3, -6 and -7). As their name indicates, initiator caspases are involved in the activation of the apoptotic pathway, while effector caspases mediate the signaling amplification loop leading to the generation of the morphological apoptotic features.[1]

Apoptosis initiates through two pathways: the extrinsic pathway (also known as death receptor pathway) and the intrinsic pathway (mitochondrial signaling pathway). The extrinsic pathway is mediated by the engagement of death receptors—transmembrane proteins belonging to the tumor necrosis factor receptor superfamily (TNFRs)—with their associated ligands (e. g. the association of TNF-α with its cognate receptor). After this, proapoptotic cellular transduction signaling is initiated by the formation of DISC (death-inducing signaling complex), which is formed by the recruitment of adapter proteins, such as FADD, TRADD or RAIDD, to the intracellular domain of the activated death receptor. After that, the initiator caspase-8 associates with the DISC and undergoes autocatalytic activation. Conversely, the intrinsic pathway is initiated by several stimuli, such as irradiation, growth factors withdrawal, and antineoplastic drugs, among others. These stimuli compromise the integrity of the mitochondrial outer membrane, fomenting the mitochondrial outer membrane permeabilization (MOMP), and releasing several proapoptotic mitochondrial proteins such as cytochrome-C (Cyt-c). This point is known as the point of no return due to the loss of mitochondrial energy-generating function. Once Cyt-C is relocated to the cytosol, it can associate with APAF1, caspase-9, and ATP, assembling the *apoptosome*. Similar to caspase-8 in the extrinsic pathway activation, caspase-9 is activated by autocatalysis in the apoptosome. Once initiator caspases are activated (from the extrinsic or intrinsic pathway), they induce the activation of effector caspases through their cysteine protease activity. Finally, the effector caspases are implied in the generation of both biochemical and morphological apoptotic features such as cellular shrinkage, bleeding, chromatin condensation, DNA fragmentation and cellular fragmentation into membrane-bound apoptotic bodies.[1,2]

2. Apoptosis regulation is lost in cancer

The caspase activity threshold dictates several cell fate decisions. In some cases, suppression of apoptosis through caspase inhibition is needed for tissue and organism health. For example, it is important in cells with low regenerative potential such as neurons and cardiomyocytes.[3] On the other hand, higher levels of caspase activity balance the cellular choice toward apoptotic program targeting unwanted cells, or damaged ones, for a clean elimination. Thus, apoptosis inhibition in damaged cells is a feature in several diseases such as cancer.[4,5] Since cancer is a group of diseases that accounts for more than 100 distinct pathologies from different organs,[6] the understanding of the underlying mechanisms implied in apoptosis inhibition is needed for the development of new antineoplastic options. In this sense, it is important to describe the apoptotic brakes.

The apoptotic pathway is a highly regulated process at different levels. If we focus on the inhibition or repression of caspase activation, there are at least three levels of regulation, taking MOMP as a reference point. First, in the extrinsic pathway, which is upstream to MOMP, cFLIP mediates the inhibition of caspase-8 activation through its displacement of the DISC. Recently, it has been described that cFLIP isoforms regulate caspase-8 activation in a co-operative and hierarchical fashion.[7] Second, at the mitochondrial level, Bcl2 family members modulate the release of mitochondrial proapoptotic proteins into the cytoplasm by the regulation