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Research article

# Striatin translocates to the cytosol of apoptotic cells and is proteolytically cleaved in a caspase 3-dependent manner

Moni Nader [a,b,*], Bariaa Khalil [a], Wejdan Kattuah [a], Nduna Dzimiri [b], Dana Bakheet [b]

[a] Department of Physiological Sciences, College of Medicine, Alfaisal University, Riyadh 11533, Saudi Arabia
[b] Department of Genetics, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia

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ABSTRACT

Striatin (STRN) is a multivalent protein holding great therapeutic potentials in view of its interaction with dynamic partners implicated in apoptosis. Although striatin-3 and striatin-4, that share high structural similarities with STRN, have been linked to apoptosis, the dynamics of STRN in apoptotic cells remain unclear. Herein, we report that the amount of STRN (110 kDa) is reduced in apoptotic cells, in response to various chemotherapeutic agents, thereby yielding a major polypeptide fragment at ~65 kDa, and three minor products at lower molecular weights. While STRN siRNA reduced the 65 kDa derivative fragment, the overexpression of a Myc-tagged STRN precipitated a novel fragment that was detected slightly higher than 65 kDa (due to the Myc-DDK tag on the cleaved fragment), confirming the cleavage of STRN during apoptosis. Interestingly, STRN cleavage was abrogated by the general caspase inhibitor Z-VAD.fmk. Cell fractionation revealed that the STRN pool, mainly distributed in the non-cytosolic fragment of naïve cells, translocates to the cytosol where it is proteolytically cleaved during apoptosis. Interestingly, the ectopic expression of caspase 3 in MCF-7 cells (deprived of caspase 3) induced STRN cleavage under apoptotic conditions. Inhibition of caspase 3 (Ac-DEVD-CHO) conferred a dose-dependent protection against the proteolytic cleavage of STRN. Collectively, our data provide cogent proofs that STRN translocates to the cytosol where it undergoes proteolytic cleavage in a caspase 3-dependent manner during apoptosis. Thus, this study projects the cleavage of STRN as a novel marker for apoptosis to serve pharmacological strategies targeting this particular form of cell death.

## 1. Introduction

Various chemotherapeutic agents have been widely used to target the apoptotic machinery in cancer therapy, but the development of a globally effective treatment is still far from being reached [1, 2]. This owes to the incomplete understanding of the complicated process of apoptosis, including the dynamics of caspases and their substrates in the cell.

Striatin is a multivalent protein that was originally characterized in rat brain synaptosomal fractions [3]. The striatin family of proteins comprises striatin-1 (STRN), striatin-3 (SG2NA) and striatin-4 (Zinedin) encoded by different gene loci, but sharing structural similarities at the protein level [4]. All three striatins are part of the evolutionary conserved multiprotein complex, STRIPAK (Striatin-Interacting Phosphatase and Kinase) [5, 6]. This complex includes the Germinal Center Kinase (GCK), the GCKIII subfamily sterile 20-like kinases (MST), and the Cerebral Cavernous Malformation-3 protein (CCM3); all of which are implicated in regulating the apoptotic process [7]. Accumulating evidence also indicate that both STRN-3 and -4 regulate apoptosis. For instance, STRN-3 provides protection against apoptosis by influencing the DJ-1/Akt pathway in Neuro2A cells [8], or through direct binding to PP2A A subunit to negatively regulate MST-3-induced apoptosis [9]. Similarly, silencing the STRN-4 gene induces apoptosis in KP4, PK9 and HCT116 cells [10]. Not only does STRN share high structural similarities with STRN-3 and -4, but it also contains binding domains to molecules (Calmodulin, caveolin-1 and -3, as well as PP2A) that are implicated in regulating apoptosis [4, 11, 12, 13, 14, 15]. Nonetheless, STRN interacts with the oncosuppressor Adenomatous Polyposis Coli (APC) which is a substrate for caspases in apoptotic cells [16, 17]. Furthermore, STRN interacts with, and serves as a target for a member of the Poly-ADP ribose polymerase (PARP) family, tankyrase1, that negatively regulates PAPR and consequently prevents cell death [18, 19, 20]. Thus, studies have linked the binding partners of STRN to cell death via apoptosis.

Despite the high structural similarities between the three members of the STRN protein family, as well as the role of their partners in apoptosis,

* Corresponding author.
*E-mail address:* mnader@alfaisal.edu (M. Nader).

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the dynamics of STRN in the context of apoptosis has not been evaluated yet. Herein, we focused our study on the dynamic of STRN in apoptosis and we report that STRN polypeptides are proteolytically cleaved during apoptosis. We also show that STRN is preferentially compartmentalized in the cytosol, in response to apoptotic stimuli, where it undergoes a caspase 3-dependent cleavage.

## 2. Materials and methods

### 2.1. Cell Culture

HeLa and MCF-7 cells were purchased from ATCC and propagated according to the manufacturer's protocol in Dulbecco's Modified Eagle Medium (DMEM), high glucose (ThermoFisher, Cat #11960044), supplemented with 10% fetal bovine serum, 1% L-glutamine, and 1% penicillin-streptomycin antibiotics (Sigma, cat #6784). Cells were passaged and propagated in 10 cm dishes with constant medium changing (every other day), and they were maintained in an incubator at 37°C and 5% $CO_2$ to the desired confluency before undergoing transfection and/or pharmacological treatment.

### 2.2. Induction of apoptosis and pharmacological treatment

To induce apoptosis, cells were serum-starved for 18 h prior to the exposure to either one of the following drugs: 1μM staurosporine (STS) (Cell Signaling, cat #9953), 100 μM etoposide (Sigma, cat #33419-42-0), or 1 μg/ml TNF-related apoptosis-inducing ligand (TRAIL) (Abcam, cat #ab55764) for different time periods as indicated in the figure legends. For assays where caspase inhibitors were employed, cells were pre-treated for 1 h (1hr) with either 10 μM of the general caspases inhibitor Z-Val-Ala-Asp-FMK (Z-VAD.fmk, MP Biomedicals, LLC, cat #03FK05001), or with the specific caspase 3 inhibitor (Ac-DEVD-CHO, Calbiochem, cat #CAS169332-60-9), prior to induction of apoptosis by STS. The development of apoptosis was identified by the inspection of the structural changes of the cultured cells (blebbing) and was confirmed by the assessment of the cleavage of caspase 3 and PARP, as well as by the release of mitochondrial cytochrome C in the cytosol.

### 2.3. Knockdown of striatin using siRNA

Transfection of the cultured Hela cells with STRN siRNAs was carried out using lipofectamine 2000 (ThermoFisher Scientific, Cat# 11668019) as described by the manufacturer. The siRNAs used were non-target siRNA-Ctrl siRNA (siRNA Negative control kit, Cat# 12935100), siSTRN-1 and siSTRN-2 (Stealth siRNAs against human STRN, Cat# 1299001) all purchased from ThermoFisher Scientific. Cells were seeded to 70–90% confluency for the transfection. The transfection was repeated after 24 h to enhance the magnitude of STRN knockdown. Cells were further incubated for an additional 24 h after which they were treated as indicated.

### 2.4. Overexpression of Myc-DDK-tagged STRN and caspase 3 in cultured cells

The plasmid used to overexpress STRN in cultured cells was Myc-STRN (Myc-DDK-tagged human STRN, Origene, cat# RC515098). As a control plasmid, we used the same vector lacking the human sequence of STRN, referred to as Myc [pCMV6-Entry (C-terminal Myc and DDK tagged), Origene, cat# PS1000]. With respect to the ectopic expression of caspase 3 in MCF-7 cells (deprived from endogenous caspase 3), a plasmid coding for the active form of caspase 3 (pcDNA3-Casp3-myc, Addgene, cat #11813) was used along with a control plasmid (pcDNA3) lacking the caspase 3 sequence. The transfection of these plasmids in cultured cells was completed using lipofectamine 2000, and according to the manufacturer's protocol.

### 2.5. Protein extraction and Western blotting

Protein extraction from cultured cells and Western blot analysis were performed as previously described [11]. The antibodies used were against STRN (BD Biosciences, cat #610838), α-tubulin (Sigma, cat #T9026), cytochrome C (Abcam, cat #ab13575), PARP (Cell Signaling, cat #9542L), cleaved caspase 3 (Cell Signaling, cat #9664L), GAPDH (Santa Cruz, cat # SC-25778) or actin (Santa Cruz, cat # SC-8432). Blots were further exposed to the appropriate HRP-conjugated secondary antibodies (Cell Signaling) and were visualized using enhanced chemiluminescence (ECL) detection reagent (GE Healthcare, cat #RPN2232). Densitometry analysis of the protein bands was carried out using the image J software.

### 2.6. Cell fractionation

Extraction of the cytosolic and non-cytosolic fractions from cultured Hela cells was carried out as previously described [21]. Both the cytosolic and non-cytosolic fractions were cleared at 10,000 g, 5 min, and 4°C to remove cell debris, and the supernatant was used for western blot.

### 2.7. Statistical analysis

Statistical analysis was performed using the Prism software version 7.0 to compare samples of at least $n = 3$ independent experiments. $P < 0.05$ was considered statistically significant using Student's t-test or one-way ANOVA test, as indicated in the figure legends.

## 3. Results

### 3.1. STRN is cleaved in apoptotic Hela cells

To explore the dynamics of STRN during apoptosis, serum-starved Hela cells were treated with STS for 3 h. Data revealed a decrease in the expression of the STRN polypeptides (~110 kDa) in STS-treated cells and the appearance of a robust band around 65 kDa, and to less extent three other bands at lower molecular weight that were slightly detected by the monoclonal anti-STRN antibody (Figure 1A). To confirm that STRN reduction is phenotypically related to apoptosis, we challenged the cells with etoposide (Topoisomerase II inhibitor; another activator of the intrinsic apoptotic pathway) or TRAIL (Activator of the extrinsic apoptotic pathway) and noticed similar effects to the ones noted following the STS insult (Figure 1B). Reaching an irreversible mode of apoptosis was also confirmed by the detection of the cleaved caspase 3 (17 kDa) and PARP (85 kDa) in apoptotic cells, and by the microscopic features of apoptosis (rounded cells) in Figure 1C.

Silencing the STRN gene indicated reduced expression of the full-length STRN polypeptides (~110 kDa), as well as the novel 65 kDa band, and the 3 other polypeptides at lower molecular weight, in STS-treated cells (+STS). Moreover, cells overexpressing human STRN tagged with a Myc-DDK fragment (referred to as Myc-STRN), and treated with STS, carried two cleaved fragments of STRN, ~65 and 70 kDa: due to the Myc-DDK tag molecular weight (Figure 1E). Together, these data imply that the 65 kDa band is a breakdown product of the 110 kDa STRN polypeptides.

### 3.2. Inhibition of caspases reduced the proteolytic cleavage of STRN

Pharmacological inhibition of caspases using the general caspase inhibitor Z-VAD.fmk prior to STS treatment showed a significant recovery of the 110 kDa STRN polypeptide and overt regression of the 65 kDa band when compared to STS-treated cells (Figure 2A). The histogram in Panel B shows a significant reduction in the ratio of the cleaved/full STRN bands when using Z-VAD.fmk + STS as compared to the STS treatment alone. The inhibitory effect of Z-VAD.fmk was confirmed by the suppressed activation of caspase 3 (shift up in the cleaved band ~17kDa) and

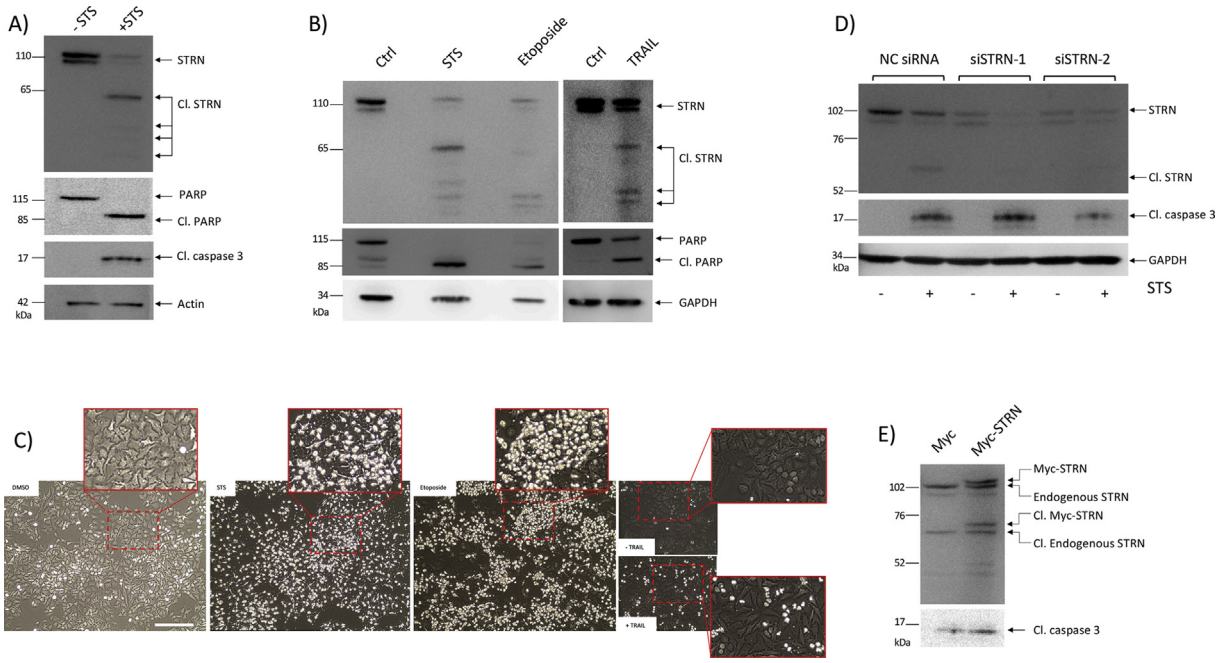



**Figure 1. Dynamics of STRN in apoptotic cells**. Representative Western blot of proteins from HeLa cells (A) treated (+) or untreated (-) with staurosporine (STS) or (B) treated with STS, etoposide, and TRAIL. C) Microscopic images (20X) of HeLa cells treated with the indicated apoptotic agents showing apoptotic features (rounded) when compared to untreated cells (DMSO as control for STS and etoposide and –TRAIL as control for + TRAIL), scale bar is 500 μm. D) Representative Western blot of proteins from HeLa cells transfected with non-coding (NC) siRNA, siSTRN-1 and -2 treated with STS as indicated or (E) overexpressing Myc-STRN or Myc-DDK alone treated with STS. Blots were probed with antibodies against STRN, cleaved caspase 3 (Cl. Caspase 3), PAPR, and actin or GAPDH for equal loading. Full-unadjusted images are shown in supplementary material (Suppl. Figure 1-A, 1-B, 1-D, and 1-E).

PARP (less 85 kDa band). Taken together, these data indicate that STRN cleavage during apoptosis is most likely mediated by active caspases.

### 3.3. Accumulation of STRN in the cytosol prior to cleavage in apoptotic cells

Since STRN is cleaved during apoptosis, we sought to verify if this cleavage takes place in the cytosol. Data in Figure 3A show that the full length STRN protein is present in both the cytosolic (C) and non-cytosolic (NC) fractions of naïve cells, with preponderance expression in the NC fraction. Surprisingly, in apoptotic cells, the STRN cleavage was more evident in the cytosolic fraction, as the cleaved band (65kDa) was hardly detectable in the NC pool of proteins (Figure 3B). Notably, the caspase 3 cleavage and the presence of cytochrome C in the cytosolic pool paralleled that of STRN. However, the knockdown of STRN had no effect on the release of cytochrome C in the cytosol (Figure 3C).

Evaluation of the time course cleavage of STRN during apoptosis revealed that this cleavage was overt at 60 min STS treatment and reached higher magnification at 120 min of STS insult (Fig 3D and E). Interestingly, the cleavage of caspase 3 along with the appearance of cytochrome C in the cytosol preceded the cleavage of STRN (starting at 30 min of STS treatment). The use of the general caspase inhibitor Z-VAD.fmk profoundly halted the abovementioned phenotypes (Figure 3D), thus indicating that the activation of caspases might be necessary for the translocation of STRN from the NC fraction to the cytosol to undergo proteolytic cleavage.

### 3.4. The cleavage of STRN is mediated by caspase 3 in apoptotic cells

Since our data showed that caspase 3 may be cleaved prior to STRN, we decided to verify if the latter is cleaved by the catalytically active caspase 3 in apoptotic cells. Therefore, we overexpressed caspase 3 in MCF-7 cells that are deprived from endogenous caspase 3. Data in Figure 4A revealed that the STS treatment did not induce a significant proteolytic cleavage of STRN in MCF-7 naïve cells. However, STRN cleavage was evident in MCF-7 cells, along with that of Casp3 and PARP, in cells overexpressing Casp3 (Fig 4A and B). Targeted inhibition of caspase 3 (Ac-DEVD-CHO) reduced the cleavage of STRN in STS-treated cells in a dose-dependent manner whereby the lowest intensity of the cleaved fragment of STRN was noticed in cells with the highest

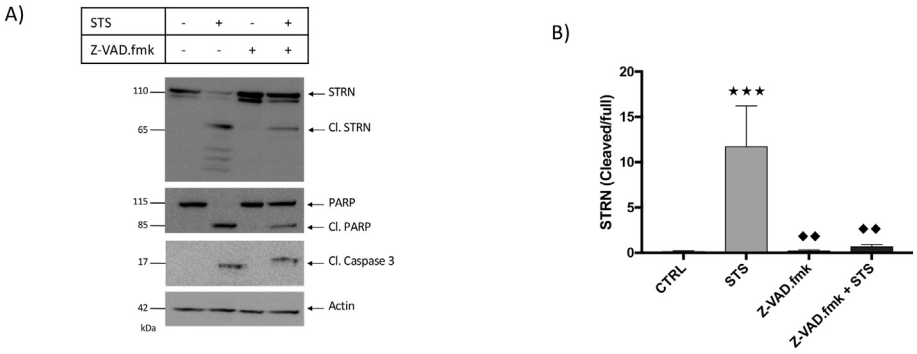



**Figure 2. Effect of Z-VAD.fmk on STRN cleavage in STS-treated HeLa cells**. (A) Example of Western blot of proteins from HeLa cells treated with (+) or without (-) Z-VAD.fmk and/or STS. Blots were probed with the indicated antibodies. B) Histogram of densitometry analysis of cleaved/full STRN bands of n = 3 independent experiments of the blots shown in Panel (A). (*) indicates p = 0.0127 when comparing the cleavage of STRN between STS and Z-VAD.fmk + STS lanes using one way ANOVA test. Full-unadjusted images are shown in supplementary material (Suppl. Figure 2-A).

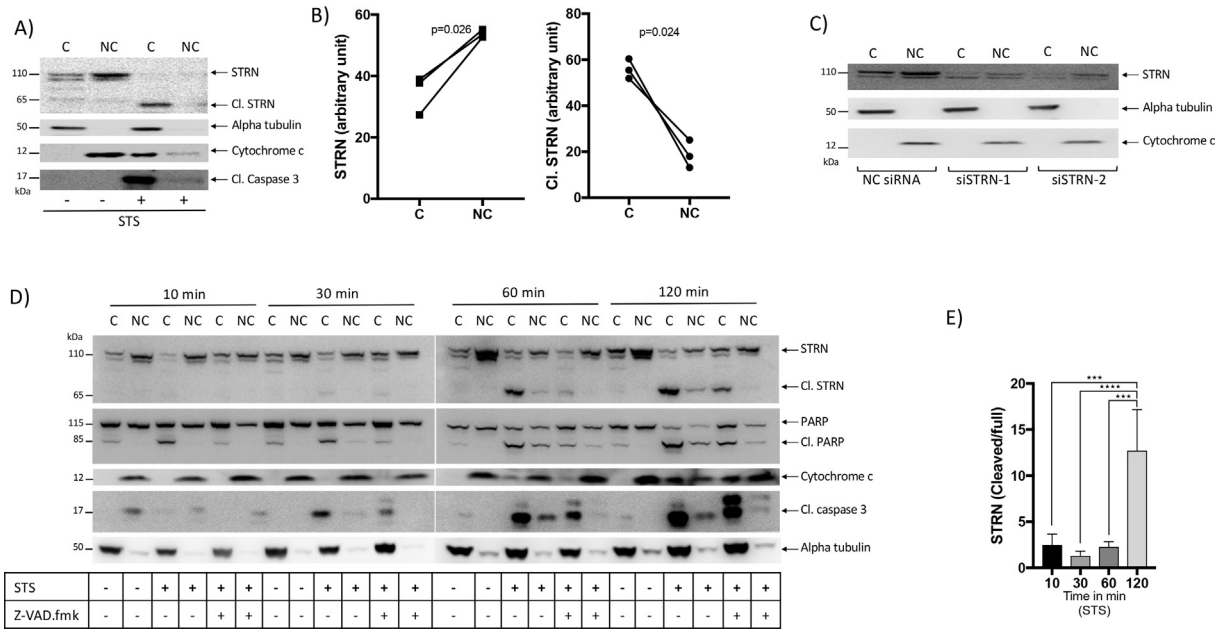



**Figure 3. Sub-cellular localization of STRN in apoptotic cells.** (A) Representative Western blot of proteins from cytosolic (C) and non-cytosolic (NC) fractions from HeLa cells treated (+) or untreated (-) with STS. (B) The graph on the left shows the full length STRN in untreated cells, and the one on the right shows Cl. STRN in STS-treated cells in both the C and NC fractions. Paired t-test was performed, and p value is indicated on the graph for n = 3 independent experiments. (C) Fractionation (C and NC fractions) of HeLa cells with silenced STRN (siSTRN-1 and -2). (D) C and NC fractions from HeLa cells treated with STS and Z-VAD.fmk at the indicated time points. Blots were probed with the specific antibodies as shown in the figure. (E) Densitometry analysis of the STRN cleavage (Cleaved/full) from the cytosolic fraction of the STS-treated cells at the indicated points from n = 4 different gels of panel D. (*) indicates p = 0.0163 using one-way ANOVA test. Full-unadjusted images are shown in supplementary material (Suppl. Figure 3-A, 3-C, and 3-D.1, 3-D.2, 3-D.3).

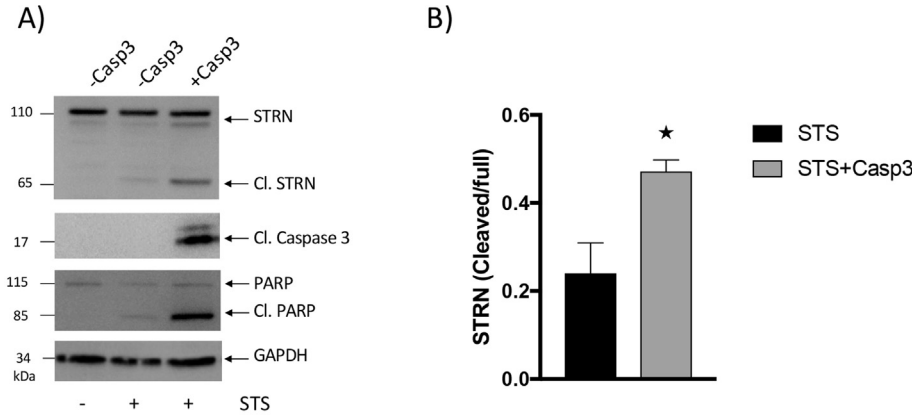
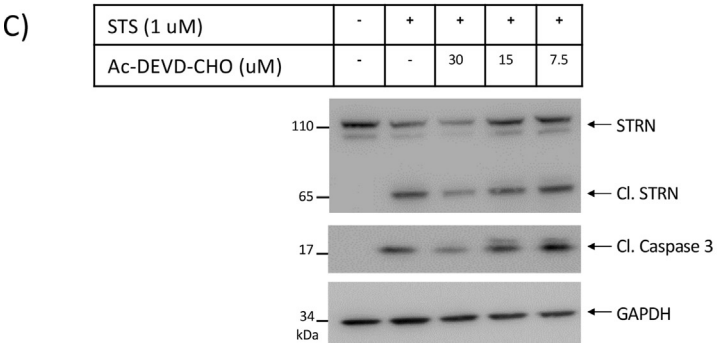



**Figure 4. Effect of caspase 3 on the cleavage of STRN during apoptosis.** (A) Representative Western blot of MCF-7 expressing caspase 3 and treated with STS as indicated. (B) Histogram representing the densitometry analysis of the cleaved/full STRN of n = 3 independent experiments. (*) indicates $p < 0.05$, statistically significant using Student's t-test. (C) HeLa cells treated with STS and the caspase 3 specific inhibitor Ac-DEVD-CHO as indicated. Blots were probed with antibodies against STRN, cleaved caspases 3 (Cl. Caspase 3), PARP, and GAPDH. Full-unadjusted images are shown in supplementary material (Suppl. Figure 4-A, and 4-C).



concentration of the caspases 3 inhibitor (Figure 4C). Collectively, our data indicate that STRN is cleaved in a caspase 3 mediated manner during apoptosis.

## 4. Discussion

We report, in this study, that STRN is proteolytically cleaved during apoptosis and that this cleavage occurs mainly in the cytosol in a caspase 3 dependent manner. This was evidenced by 1) the proteolytic degradation of STRN during apoptosis, 2) the enrichment of cleaved STRN fragment in the cytosol of apoptotic cells, 3) the required activation of caspase 3 for the cleavage of STRN, and 4) the abrogated cleavage of STRN following caspase 3 inhibition.

Our data showed that the full length STRN is invariably cleaved in response to various apoptotic agents (Staurosporine, etoposide and TRAIL). Both knockdown and overexpression approaches confirmed that the newly detected bands (using a STRN monoclonal antibody) are a breakdown of the STRN polypeptide. In fact, the overexpression of a Myc-DDK-tagged STRN protein revealed a breakdown product slightly higher than that detected at 65 kDa, due to the molecular weight of the Myc-DDK tag, thus confirming the cleavage of the Myc-DDK-STRN protein.

The list of substrates for caspases, particularly caspase 3, is relatively long and comprises various proteins involved in different cellular processes [22]. Herein, we identified STRN as a novel substrate for active caspase 3 in apoptotic cells. Interestingly, STRN proteolysis is mainly processed in the cytosol, similarly to other identified target proteins for catalytically active caspases [23]. Abrogation of the proteolytic reduction of STRN in response to pharmacological inhibition of caspase 3 (Ac-DEVD-CHO) confirmed that the STRN cleavage is caspase 3-dependent. Although the cleavage of STRN was not fully terminated by the caspase-3 inhibitor, the significant reduction in the proteolytic fragment of STRN implies that this cleavage is mainly achieved by caspase 3. Similar results support our findings while assessing for the proteolytic cleavage of the protein kinase C by caspases [24]. In addition, the overexpression of caspase 3 in MCF-7 cells (deprived of caspase 3) promoted the cleavage of STRN proteins in response to STS treatment. Together, our data provide a cogent proof that STRN cleavage is caspase 3-dependent. It is important to emphasize that the present observation is in line with a previous report indicating that both calpain-2 and caspase 3 are able to cleave STRN in a biochemical reaction *in vitro* [25], but no further evaluation of this process was performed in a cellular context. However, the molecular weight of the breakdown products yielded from the biochemical reaction differ from those detected in our conditions (cellular context). This discrepancy in the size of the cleaved STRN could be due to the internal factors that may affect the function of caspase 3 in apoptotic cells, compared to the *in vitro* reactions. In fact, supporting studies indicate that while the cleavage of MST4 (MST3 and SOK1-related kinase), a component of the STRIPAK complex, using recombinant caspases 3, 7 or 8 could not be detected *in vitro*, the recombinant MST4 was cleaved by caspase 3 in Jurkat cells [26, 27].

Our data also show that STRN translocates to the cytosol of apoptotic cells in order to undergo proteolytic cleavage. In fact, we observed that the non-cytosolic fraction initially contained higher amounts of STRN than the cytosol of naïve cells. However, during apoptosis we found that only a small amount of STRN could still be recovered in the non-cytosolic fraction, while the greater part was detected in the cytosol, accompanied by a more pronounced cleavage of STRN in the cytosolic fraction. This scenario implies that during apoptosis STRN translocates to the cytosol where it undergoes cleavage, similar to other caspases or proteins [28]. In fact not only do caspases redistribute within the cellular compartments, but also their substrates (native form or cleaved part) target different organelles (i.e. Golgi apparatus, nucleus, cytosol and mitochondria) [23]. For example, adenylate kinase-2 is usually released from the mitochondria into the cytosol in apoptotic cells; hence STRN might have been also released from subcellular organelles to undergo cleavage in the cytosol [29, 30]. Similarly, while caspase 3 precursors are found in the cytosol and mitochondria, caspase 3 activity is mainly confined to the cytosol during apoptosis [31, 32]. Consistent with these premises, the time course assessment of caspase 3 activity and STRN cleavage showed that caspase 3 activity in the cytosol preceded the cleavage of STRN, thus suggesting the implication of the former in its proteolytic degradation.

In conclusion, we provide substantial proof demonstrating that STRN translocates to the cytosol of apoptotic cells, where it is proteolytically cleaved in a caspase 3-dependent manner. We also crystallize STRN as a novel marker for apoptosis. This data enhances our current knowledge on the dynamic of STRN and its subcellular distribution during the onset and progression of apoptosis and paves the way for deeper investigation to evaluate the role of STRN in regulating caspase 3-dependent apoptotic signals.

## Declarations

### *Author contribution statement*

M. Nader, B. Khalil and W. Kattuah: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

N, Dzimiri: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

D, Bakheet: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

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### *Competing interest statement*

The authors declare no conflict of interest.

### *Additional information*

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