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REVIEW

Recent progress in apoptosis triggering facilitated by HeLa Studies

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Objective: Cancer is a leading cause of death globally, prompting numerous efforts to find effective treatments. HeLa cells, derived from Henrietta Lacks' cancerous squamous cells, have played a crucial role in cancer research due to their origin, resistance, and rapid growth. They are particularly useful for studying ways of cellular death triggering, or apoptosis, without an immune response. Thus, the objective of this paper was to review the latest publications on the subject of HeLa apoptosis so that a brief view to be available on the otherwise so extended subject. **Methodology**: To provide a concise review of the extensive research on this topic, a search was conducted using the phrase "HeLa cells apoptosis triggering" on PubMed. The articles that were published in English, in the last 6 years, presenting results sustained by valid morphological and chemical apoptotic changes present in cells, were selected and reviewed. A comprehensive table presenting the apoptotic mechanism exerted by each substance was made to assure a concise presentation of the results. **Results**: The reviewed studies have shown that many natural substances exhibit pro-apoptotic activity on malignant cells and can be used as chemotherapeutic agents. Some synthetic molecules were showed to have good results too. Important facts about these substances, their intervention site and metabolic modifications are presented in a concise form. The use of nano-carriers for targeted delivery was shown to increase their specificity towards cancerous cells.**Conclusions**: HeLa cells were a groundbreaking discovery that revolutionized scientific research. Although there is ongoing research towards cancer cures using HeLa cells, there are still many trials and considerations that need to be addressed. With the countless existing HeLa cell lines, the scientific possibilities for research are endless.

Keywords: HeLa cells, apoptosis, malignant, cancer

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Introduction

Nowadays, cancer represents a main point of interest for the scientific community since it is the second deadliest health-related problem [1-5]. The enormous number of studies regarding possibilities of intervention mostly use what Henrietta Lacks offered to the world, her precious cells, as work ground. In 1952, based on Henrietta's cervical adenocarcinoma cells, the first sustainable cell culture was established. Named HeLa, after her initials, the line presents malignant modifications, thus making it perfect for cancer studies. Due to frequent divisions and chromosomal instability, an uncertain amount of different HeLa lines exists [1].

Unmutated cells have a programmed life span, which culminate by apoptosis triggering. This type of cell death can be started not only by senescence factors but also by activation of different pathways in case of cellular damage or unproper functionality [4,5]. Unfortunately, malignant cells are ''immortal" meaning that they do not undergo this physiological death, no matter how badly altered their normal functions are [5]. Looking for a way to cure or at least treat cancer, scientists have seen a great opportunity in apoptosis triggering, since it is the most effective and harmless way of eliminating unwanted cells [2]. In order to determine the precise location for intervention within the apoptosis mechanism, it is necessary to have a comprehensive understanding of the entire molecular process.

Apoptosis has two possible activation pathways, an intrinsic one, based on mitochondrial-related activity, and an extrinsic one, centered around the death receptor activation. The key step towards the end of the cell life is Caspase activation, which is achieved by both pathways [4,5]. A functional and quantitative balance of proapoptotic and anti-apoptotic proteins should be maintained for the cell proper functionality. The majority of these proteins belong to the Bcl-2 protein family, which contains both apoptosis-sustaining ones (Bax, Bak, Bok) and also the opposing proteins (Bcl-2, BCLx, Bclw). A functional or quantitative modification in favor of the pro-apoptotic ones usually leads to apoptosis of affected cells [4,6].

A lot of substances have been reported to induce apoptosis, in different ways, like luteoloside, magnolol or eugenol for example. Given the high number of articles and emerging strategies available, it is essential to conduct a review to fully comprehend and make use of all the information, thereby facilitating the development of a final product for improved cancer management

Methodology

A search through PubMed database was conducted, using the following targeted phrase "HeLa cells apoptosis triggering". As the aim of the paper was to provide a viewpoint on

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the most recent approaches and underlying mechanisms of apoptosis induction in HeLa cells, articles for this review were selectively chosen from publications within the last 6 years. Selection criteria included free accessibility and the language of writing, which was limited to English. In the screening process, we eliminated all the articles that did not have complete description of the apoptotic events following the administration of substances. Since we wanted to select only the most relevant results, we considered eligible for reviewing only the articles that were presenting cells undergoing apoptosis after substance administration, excluding the ones that were related to other types of cellular death. The purpose was to select only the articles that led to a substantial diminish in cellular mass, so we selected only the articles that presented the apoptotic outcome quantitatively (Figure 1).

Apoptosis and how it can be triggered

A wide range of substances were found in the past few years to have apoptotic effects on different malignant cells, almost each of them with a different mechanism regarding the completion of the process. Most experiments started from the known phases of apoptosis, with the goal of finding a target element where the process could be activated. From the selected articles we extracted a short presentation of the main apoptotic events (Tabel I).

Looking at the intrinsic apoptosis pathway, caspase cascade is the main step to be achieved and it is activated by Caspase 9. To activate Caspase 9, a cytoplasmatic apoptosome must be constructed using both cytochrome c and APAF1 (apoptotic protease-activating factor 1) as key components. However, approximately 80% of cytochrome c is stored between the mitochondrial membranes. Large pores must be formed in the MOM (mitochondrial outer membrane) for cytoplasmatic release of cytochrome c [2,7]. This can be achieved by modifying the balance between the pro- and anti-apoptotic members of the BCL-2 family. Bax plays a critical role as a major regulator in facilitating the increase of mitochondrial membrane permeability. BCL-2 helps maintaining the mitochondrial integrity, protecting them against cell apoptosis [2,7,8]. Inside the mitochondria, p53 has the ability to initiate the intrinsic apoptotic pathway by directly binding to and disabling certain mitochondrial anti-apoptotic proteins (namely Mcl-1, Bcl-2, and Bcl-XL) and stimulating pro-apoptotic effector proteins (specifically Bak and Bax), thus determining apoptosis [8,9].

Extrinsic apoptosis is different from intrinsic apoptosis because it involves the activation of death receptors, which are a subset of the TNFR (tumor necrosis factor receptor) superfamily and represent a type I transmembrane protein. After binding with a particular ligand, the death receptor changes its DD (death domain) configuration to bring together other cytoplasmic proteins containing DDs. This creates a platform that can either promote cell survival through NFκB (Nuclear factor kappa-light-chain-enhanc-

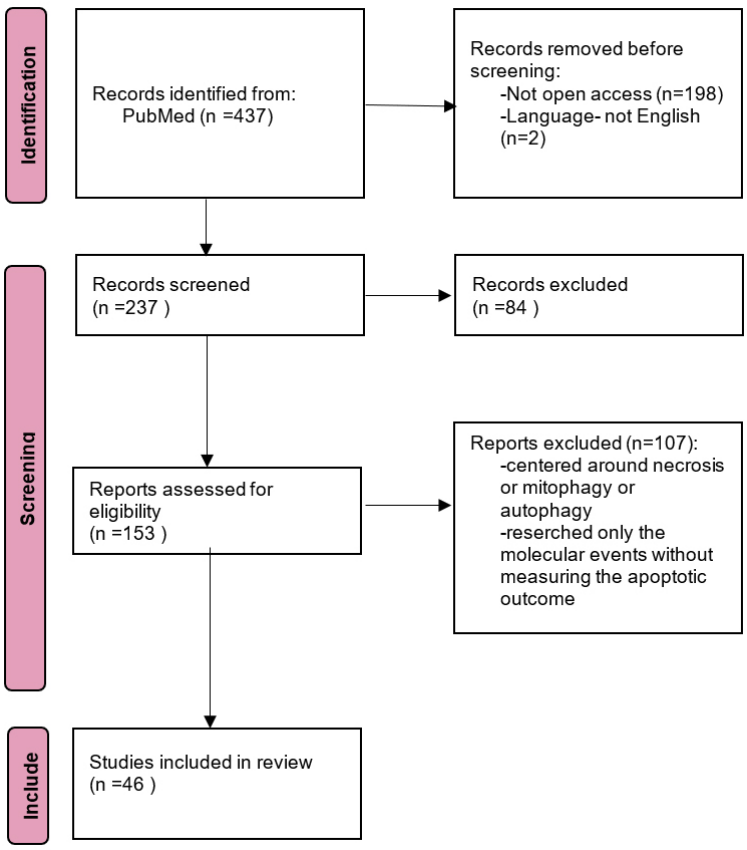

Fig. 1. Preferred reported items for systematic reviews and meta-analyses (PRISMA) flow diagram suggesstive for the process of article selection from the PubMed database between 2017-2023 regarding HeLa cells apoptosis triggering

Table I. A synthesis of the substances found to trigger apoptosis and their molecular mechanisms of action

Author	Year	Substance	Intervention Site	Metabolic modifications
Pawar JS et.al [8]	2022	Chrysin and Capsaicin	ROS	ROS ↑, p21, p53, and p16 protein overexpression, Bax ↑, Caspase 3↑, Bcl-2 ↓
Yuming Zhang et.al [9]	2022	Resveratrol	mitochondria	ROS ↑, mitochondrial respiratory capacity ↓,
Zeng Z et.al [10]	2021	Dinuclear copper(ii) complexes with thiazole ligand	ROS, DNA	G0/G1 stage arrest
Álvarez-Ortiz P et.al. [11]	2021	Purshia plicata compounnds	Apoptotic proteins	Bcl-2 ↓, HSP70 ↑, cytochrome c ↑, p53 ↑, APAF1 ↑, caspase 3 ↑
Enrique Ortega-Forte et.al. [12]	2021	COUPY Coumarins	ROS	ROS production, specifically peroxyl radicals
Pandey S et.al. [13]	2021	Sulfonohydrazide-hydrazone molecules	Endoplasmic reticulum	Endoplasmic reticulum stress
Xiong C. et.al. [14]	2021	Morchella importuna peptide	mitochondria	Mitochondrial membrane potential ↓, cytosolic cytochrome c ↑, Bax ↑, Bcl-2 ↓, activated Caspase 3 ↑
Xu G. et.al. [15]	2021	Glucocappasalin	CDK &PLK	Cyclin B1 ↓, CDK1 ↓, phospho- CDK1, p21 and p27 significantly upregulated, Bcl-2 and Bcl-xL ↓, G2/ M cell cycle arrest
Raina R. et.al. [16]	2020	Luteolin	Akt/mTOR and MAP kinase pathways	BCL2 and MCL-1 ↓, increased expression of TNF RI/TNFRSF1A, FADD, p-p53 (S392), TRAIL R2/DR5, p-RAD-17 (S635), HSP27, Fas/TNFRSF6/CD95 , TRAIL R1/DR4, p-Rad17 (S635) ; downregulation of BCL-X, Pon2, p27/ Kip1, HIF-1α, BCL2, cIAP-1, cIAP-2, Clusterin , Claspin and XIAP
Xu L. et. al. [17]	2020	IU-1	MDM2 gene	G0/G1 arrest, ↑ fractions of caspase 3, 8 and 9, p53 and MDM2 regulation,
Chandrasekaran AP et. Al. [18]	2020	YM155 and TRAIL	Survivin inhibitor	↓ c-FLIP, ↓ survivin, ↑ cleaved caspase 3 fraction
Zhou M et.al. [19]	2020	12-Deacetyl-12-epi-Scalaradial	Nur 77 & MAPK/ERK Pathway	↑ cleaved PARP, caspase 3 and 8 activation, ↓ level of ERK phosphorylation, deactivation of MAPK/ERK pathway, little modulation of Nur77
Lin R et.al. [20]	2020	Naringin	β-catenin pathway	cell cycle arrest at a G0/ G, ↑ phosphorylation of p-eIF2α and p-PERK, ↑ caspase 3, ↑E-cadherin, ↓ vimentin
Kavčič N et.al. [21]	2020	leucyl-leucine methyl ester	Mitochondria and Cathepsin C	↑ cleavage of Bid, ↑ lisosomal cathepsin release, caspase activation, degradation of anti-apoptotic Bcl2 proteins
Armentano B et.al [22]	2020	5-(Carbamoylmethylene)-oxazolidin-2-ones	Cyclins and CDKs Mitochondria path	↑activated caspase 9, ↓MMP, ↑ROS, cytochrome c release, cell cycle arrest in G1, ↓ phosphorylated Rb protein and cyclin D1
Tian Q et.al. [23]	2019	Scopoletin	PI3K/AKT pathway	↑Caspase 3, ↑Caspase 8, ↑Caspase9, membrane blebbing and DNA damage, G2/M cell cycle arrest, ↑PARP, ↑Bax, ↓Bcl-2, ↓ phosphorylation of p-AKT and p-PI3K
Li D et.al. [24]	2019	17-b-Estradiol (E2)	Schlafen 12	↓Bcl-2 and Mcl-1, ↑activated caspase 3 and 7, ↑ cytochrome c in cytosol, PARF cleavage
Zhao Q et.al.[25]	2019	Melatonin (in presence of TNFα)	CaMKII/Parkin/mitophagy axis	Mitophagy arrest, CaMKII pathway inhibition, Parkin downregulation, ↑Caspase 3 and Caspase 9 activity
Jakovljević K et.al. [26]	2018	1,3,4-thiadiazole–chalcone	mitochodria	G2/M cell cycle arrest; Caspase 3, 8 and 9 activation
Han YQ et.al. [27]	2018	Myostatin knockout	ROS	↑ fatty acid oxidation, ↑ ROS, caspase activation
Hasson SS et.al. [28]	2018	Aucklandia lappa Decne	DR4 and ROS	activation of death receptors, DNA fragmentation, activation of caspase 3, DFF40 endonuclease activation
Shao J et.al. [29]	2018	Luteoloside	MAPK and mTOR Signaling Pathways	↓ phospho-mTOR and Bcl-2, ↑cleaved PARP, ↑phospho-p38, ↑p53, ↑FAS, ↑ Bax, ↓MMP, Caspase 3 activation ↑cytosolic cytochrome C, ROS decrease
Zhang FZ et.al. [30]	2018	Triptolide	HSP90β	site-specific phosphorylation of HSP90β, G1 cell cycle arrest, CDK4 ↓, ↑ PARP cleavage, Caspase 3 activation, ↓Rb fosforilation
Wang W et.al. [31]	2018	Mitofusin-2	mitochondria	↓MMP, ↑ activated Caspase 3 and Caspase 9, ↓ Bcl-2/Bax ratio, ↑ p53 expression
Wang DD et.al.[32]	2018	SAP	mitochondria	↓Bcl-2, ↑cytochrome c, ↑Bax, ↑caspase 3 and 9
Jaudan A et.al. [33]	2018	Pinostrobin	ROS production	↓MMP, ↑ROS, ↑ cytochrome c, ↑Bad, ↑SMAC/Diablo, ↑Bax, ↑Fas, ↑TRAIL R1, ↑FADD, ↑ TRAIL R2
Plissonnier ML et.al. [34]	2017	Ciglitazone	TRAIL sensitivity	↑DR 4 ad DR 5 expression, caspase cascade activation, ↓c-FLIP, ↓E6 viral oncoprotein, ↑ROS, ↑p53
Xu T et.al.[35]	2017	Betulinic acid	PI3K/Akt pathway	↑Bad, ↑Caspase 9, ↑ROS, ↑ p27Kip and p21Waf1/Cip1, G0/G1 phase cell cycle arrest, ↓MMP
Singh PK et.al. [36]	2017	Dynein light chain 1	Bim; Mcl-1	Formation of DLC1–Bim–Mcl-1 complexes, ↑apoptotic protein interactions
Zhu X et.al. [37]	2017	brefeldin A tunicamycin thapsigargin (TG)	NF-κB factor	Caspase 12 activation, ↑IRE1a, ↑GRP-78, ↑ unfolded protein response
Cheriyamundath S et.al. [38]	2017	(Z)-Ethylidene-4, 6-Dimethoxycoumaran-3-One	unknown	Specific apoptotic morphology, DNA fragmentation
Souza RP et.al. [39]	2017	Apigenin	Intrinsic pathway	↓MMP, ↑ROS,
Woldetsadik AD et.al. [40]	2017	pHK-PAS	HKII	release of cytochrome c, ↓MMP, ↓ATP,
Zhang W et.al. [41]	2017	NADA	E6/E7	↓survivin, ↓Bcl-2, ↓Bcl-1, ↑Bax, ↑Bak, ↑activated Caspase 3 and 9, ↓MMP, ↓E6, ↓E7, ↑ROS
Sophonnithiprasert T et.al. [42]	2017	Goniothalamin	ER stress induction	G2/M cell cycle arrest, ↑p38, ↓MMP, cytochrome c release, ↓Bcl-2, ↓Bcl-1, ↑Bax,

ROS-reactive oxygen species, Hsp70- heat shock protein 70, SAP- novel polysaccharide extracted from Sarcodon aspratus, PARP -poly ADP-ribose polymerase, Fas- factor associated suicide, c-FLIP - FLICE-Like Inhibitory Protein, UPS- ubiquitin-dependent proteasome system, HSP90β - heat shock protein 90 beta, CDK1- cyclin-dependent. kinase 1, CDK4-cyclin-dependent kinase 1, PLK1- polo like kinase 1, MDM2- Murine double minute 2, R2/DR5- death receptor 5 mTOR - mammalian target of rapamycin, DFF 40- DNA Fragmentation Factor 40, IRE1a- endoribonuclease inositol-requiring enzyme 1 α, GRP-78- Glucose-Regulated Protein 78, SMAC- Second mitochondria-derived activator of caspase, DIABLO- Direct Inhibitor of Apoptosis-Binding protein with LOw pI, TNFα- tumor necrosis factor alpha, Mcl-1- Myeloid leukemia 1

er of activated B cells) signaling or initiate programmed cell death through apoptosis [4,16]. The message is processed through a signaling system that involves MAPK (mitogen-activated protein kinase), NFκB, and PCD (programmed cell death) before a decisive action is taken. NFκB facilitates cell survival by transcription of pro-survival genes, including cytokines and chemokines, while the PCD pathway promotes programmed cell death. MAPK evaluates the situation thoroughly before determining if fighting for survival is necessary [4,29]. This results in the recruitment and rapid activation of caspase 8. Once activated, caspase 8 can cleave Bid, leading to the release of cytochrome c from the mitochondria and the subsequent activation of caspase 9 in conjunction with APAF-1. Both caspase 8 and 9 then activate caspase 3, the primary initiator of apoptotic DNA fragmentation, ultimately leading to cancer cells apoptosis [4,19,37]. In contrast, FADD (FAS-associated via death domain) is the sole adapter protein authorized to directly initiate programmed cell death. FADD comprises a death effector domain (DED) that corresponds to the same structures in Caspase 8 and 10, thereby directly activating caspases [4,15,33].

Survivin

Survivin is a molecule with anti-apoptotic properties that is typically upregulated in cancerous cells. YM155 (Sepantronium Bromide) is a survivin inhibitor that was specifically developed to treat cancer. Multiple preclinical studies and phase I/II clinical trials have demonstrated its efficacy in inhibiting survivin. In HeLa cells, YM155 increased sensitivity to TRAIL-mediated apoptosis and reduced both the mRNA and protein expression levels of surviving [18].

MAPK pathway

Luteolin is a flavone that can be found in various vegetables and fruits, such as carrots, celery, artichokes, and parsley, as well as in several spices, including thyme and oregano. Luteolin can trigger apoptosis and cell cycle arrest by suppressing the MAPK/AKT/PI3K (mitogen-activated protein kinase, protein kinase B, phosphoinositide 3-kinas) pathway, which, in the end, leads to DNA fragmentation [19].

The MAPKs phosphorylation, which is directly proportional with the fraction of phospho-JNK (phospho Jun-amino-terminal kinase) and phospho-p38, corresponds to the pathway inactivation. Luteoloside was found to raise the level of those phosphorylated proteins, thus leading to apoptosis [29,43].

The activation of Ras, a type of small GTP(guanosine triphosphate) binding protein, leads to ERK (extracellular signal-regulated kinase) signaling and downstream transcription factors is a critical step in MAPK signaling, which is facilitated by Grb2 (growth factor receptor bound protein 2). The protein Gerb is thought to play a role in linking cell surface growth factor receptors to the MAPK signaling pathway. It is believed to act as a mediator between these receptors and their downstream signaling molecules, ultimately leading to the activation of the MAPK pathway. Consequently, Grb2 plays a vital role in promoting the growth of tumor cells and inhibiting their differentiation [44].

β-catenin pathway

Naringin abrogates the β-catenin signaling pathway by inhibiting phosphorylation of β-catenin at GSK3-β (Glycogen synthase kinase-3 beta) Serine9 and Serine675 situses, thereby triggering the arrest of the cell cycle in the G0/ G1 phase [20].

Targeted delivery and photodynamic therapy

Targeted therapies hold the potential for increased selectivity and decreased toxicity when compared to conventional cytotoxic drugs. Mitochondria can be influenced in various ways to initiate cell death, which differs from traditional approach and may ultimately enhance drug efficacy in tumor cells. Nano-scale drug delivery systems have the potential to improve the effectiveness of anticancer drugs by enabling lower doses administration, concentrating the drug at the intended site, and decreasing adverse effects. The most frequently utilized nano-carriers for targeted drug delivery are liposomes. Liposomes are a favorable drug delivery system due to their biocompatibility, biodegradability, low toxicity, and capacity to encapsulate both hydrophilic and lipophilic drugs. However, a significant obstacle in liposome formulation design and processing is the encapsulation of hydrophilic drugs, as they are highly water-soluble and become dissolved in the external aqueous phase during liposome preparation [45,47].

Compared to conventional drug delivery methods, nanoparticles offer several advantages, including improved pharmacokinetics and biodistribution, enhanced drug stability and solubility, and increased bioavailability. The small size of nanoparticles also allows them to penetrate tissues and cellular barriers more effectively, improving their therapeutic potential while minimizing toxicity to healthy tissues [47].

To improve the recognition and uptake of nanoparticles by target tissues, their surfaces can be altered by attaching targeting ligands, such as folic acid, integrins, antibodies, transferrin, and polysaccharides. Among these ligands, folate receptors (FRs) are particularly useful for tumor-selective drug delivery because they are overexpressed on the surface of many cancer cells and are found with lower frequency in normal tissues [47]. Results of [45-47] were sustaining the use of this new approach in cancer treatment, as apoptosis and significant changes in the studied malignant tissues were observed.

Discussions

Conventional cancer treatments, such as chemotherapy, face a significant challenge due to the genotypic and phenotypic heterogeneity of cancer cells. These treatments

often lack selectivity and may result in non-specific cytotoxicity, limiting their effectiveness and increasing the risk of cancer recurrence [16,33,44]. In this context, scientists have found new approaches on this matter, some of which were presented in this paper. Most of the research choices were made towards natural compounds, some of them already used in local medicine as anti-inflammatory or rejuvenating substances, hoping that the apoptotic effect would just be seen in malignant cells and not in healthy cells too. Research spanning several decades has shown that dietary constituents, especially those derived from medicinal plants, have the ability to modulate the complex process of carcinogenesis by regulating gene expression and inducing apoptosis [33]. Even though this was reported in several studies, we found some flaws to some substances as well. For example, in the case of leucyl-leucine methyl ester, it was observed that monocytes exhibited greater sensitivity to the drug than malignant cells, which could be attributed to their higher intracellular levels of cathepsin C, the most upstream molecule in the pathway, when compared to cancer cells [21]. This means that the specificity of the drug is not high enough, and the damages that could be caused to the organism might not be worth taking the risk. Not all the studies and all the substances had the same rate of success in triggering apoptosis, but having a wider perspective above things helps finding the best solution to any problem.

Conclusion

Hela cells were a great scientific discovery that made an unmeasurable difference in the researcher's vision. They were the key to manufacture the Polio and HPV vaccines, the key to improve cell cultures and an important base for genetic discoveries. Someday, it might also be known as the facilitator for the cancer cure, but for the moment, even though the research towards this target has advanced rapidly, there are still many trials that need to be done and considerations to be taken. The scientific possibilities with these cells are, as the number of HeLa existing lines, unmeasurable.

Author's contribution

MTC – Conceptualization, Writing – original draft, Funding aquisition

MAB – Supervision, Writing – review & editing, Methodology

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Conflicts of interest

The authors declare no financial or other conflict of interest.

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