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Fevziye Vural
Department of Biology, Faculty of Science, Ankara University 06100 Tandoğan, Ankara –TÜRKİYE
E-mail: fevziyeduyguvural@hotmail.com

Suna Cebesoy
Department of Biology, Faculty of Science, Ankara University 06100 Tandoğan, Ankara – TÜRKİYE
E-mail: *cebesoy@science.ankara.edu.tr*

Mehmet Karakaş
Department of Biology, Faculty of Science, Ankara University 06100 Tandoğan, Ankara – TÜRKİYE
E-mail: *karakas@science.ankara.edu.tr*

Correspondence:
Fevziye Vural
Department of Biology, Faculty of Science, Ankara University 06100 Tandoğan, Ankara –TÜRKİYE
E-mail: fevziyeduyguvural@hotmail.com

Classification of Cell Death

Fevziye Vural, Suna Cebesoy and Mehmet Karakas

ABSTRACT
In 1972 Kerr and colleagues collect the cell death under two headings. Although cell death is known as apoptosis ve necrosis, molecular studies add to morphological studies and according to this, this classification is extended. In 2009 NCCD classifies it entosis, mitotic collapse, necrosis, necropitosis and pyroptosis by using terminological words. In addition to these there are diffirent types of cell death in terms of signal pathway. These are autophagic cell death, carnification cell death, netoz cell death, partanatoz cell death, anoikis cell death. In this article these types of cell death is noticed in detail.

Keywords: Mitotic Catastrophe, Pyropitosis, Cornification, Parthanatos, Anoikis

1. Introduction
In 1972 Kerr and colleagues collect the cell death under two headings. These are Apoptosis (programed cell death which is controled as genetic) and necrosis (accidental and unprogrammed cell death) [1]. Clarke [2] mentions about three major morphologies of cell death in his article dated 1990. These are type I cell death; apoptosis, type II cell death; autophagic cell death, type III cell death; non-lysosomal cell death.
Classification of cell death acquires a new dimension with establishing of NCCD (Nomenclature Committee on Cell Death) in 2005. This study is prepared by terminology which NCCD foresees. There are some things to consider for "Classification of Cell Death" by taking into account biochemical parameters. For instance, physiopathologic importance of cell death, signaling specification of cell death, using pharmacologic inhibitories or activators, determining of mutual steps between the different types of death, determining of form of death which is under control or accidentally, and finally evaluating of results with specific terminology.
In this part, types of cell death will be illuminate which are discovered recently instead of apoptosis cell death, necrosis cell death and autophagic ceel death.

2. Classification of cell death:
According to Kroemer and collegues [3] cell death is classified under four types. These are;
1. In terms of morphological appearances
2. In terms of enzymological features
3. In terms of functional phases
4. In terms of immunogenetical features

2.1 Mitotic catastrophe:
Mitotic catastrophe is specific mitosis damage on mitosis signaling pathway. In the course of mitosis remission, lethal and cytoprotective signals are come into existence. The balance failures of these signals are searced out mitotic collapse and at the same time morphological changes are occured. These morphological changes include micronucleations (arise from un equal scattered chromosomes or pieces of chromosome) and multinucleations (a lot of cells with micronucleation are paralled to "two or more cores or they occure with not separation at heterogeneous measure during cytokinesis"). After mitotic collapse apoptosis or necrosis morohologies can be observed [4] (Figure 1).

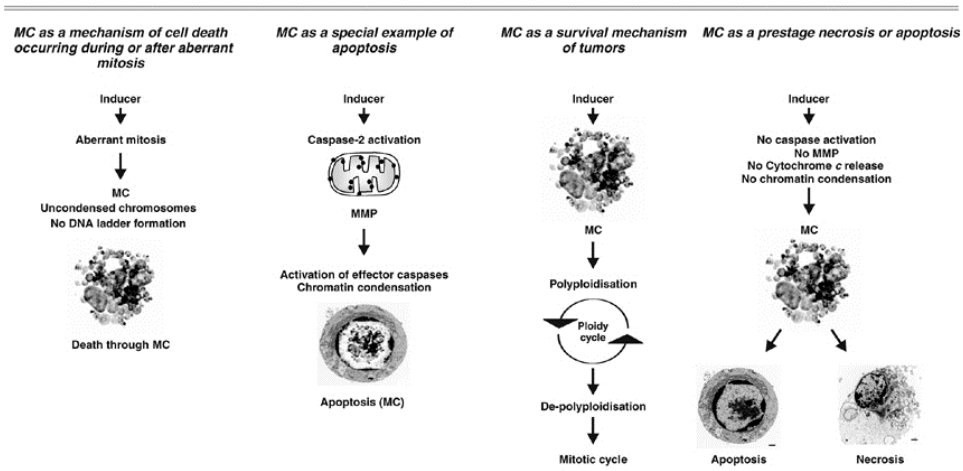
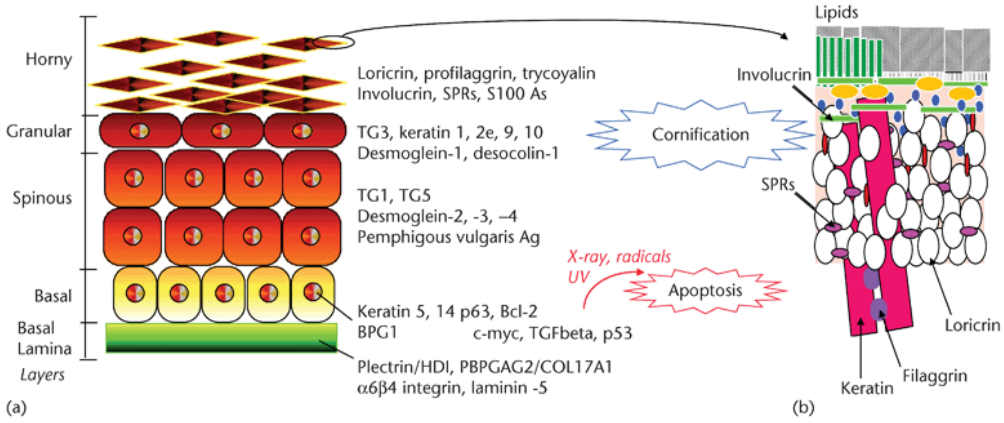


Fig 1: Death through a tragedy: mitotic catastrophe. (Vakifahmetoglu, Olsson and Zhivotovsky, 2008)

2.2 Cornification:

It occurs at the epidermis. It differs from apoptosis as morphological and biochemical. Our skins are covered by death cells. These are named corneocyte and they have important functions as physical and chemical barriers. Corneocytes are big type cells at the skin. During cornification, corneocytes lost their organelles and cores, and they die. At the end of it corneocytes Absent from the skin thereby exfoliate. It is needed cas-14 for skin formation. Cornification is considered as keratinisation or formation of keratin envelope and the terminal differentation programme is thought on the other coreless tissues (for example, lens epithelium and mature red blood cell) [5]. This case's major reason for cell death is caspases (generally limited) (Figure 2).



(c)

	G	S	K	Q	P		
CE	50.3	21.8	3.4	5.9	5.1 (%)	Epidermis	Forestomach
Loricrin	59.4	24.1	2.0	3.4	1.8	82%	65% (w/w)
Keratins	23.8	13.9	4.8	12.7	0.8	-	10%
Filaggrin	15.7	19.8	0.0	21.4	2.8	6%	5%
Involucrin	5.0	3.2	10.0	41.3	9.1	-	-
SPRs	0.4	3.8	12.4	21.6	43.6	8%	18%

Fig 2: Cornification of the skin (Candi and Melino, 2009)

By contrast with corneocytes, not only mature red blood cells but lens epithelium cells as well are talented to stop the death which is related to stres [6] and for this reason only cornification is regarded as a favorable cell death programme.

2.3 Anoikis:

Apoptosis called "anoikis" which is set off with binding loss of substrate or other cells [7]. In the proper meaning of word it means "case of being homeless". It is introduced by Frisch and its origin is Greek. In 1994 it is used [8] by Francis for representing apoptotic reply of cell in the lack of adhesion molecules at the interactive relation of cell-matrix. In very deed unchanged alive sticky cells Accommodate depending upon signals by integrins and via some growth receptors (like epidermal growth receptors) form an interaction on the extracellular matrix [9]. It is determined on the anoikis resistance epithelium cancerous cells and these cells maintain metastatic potential with spreadability. The underlying reason is that there are cascade molecules [10]. Under the functional and biochemical assessments, there is identified a sticky limited fatal cell at anoikis. It sets off spreading of matrix by the reason of lack of β1-integrin and it is charecterized by nonassociability of matrix [9] (Figure 3).

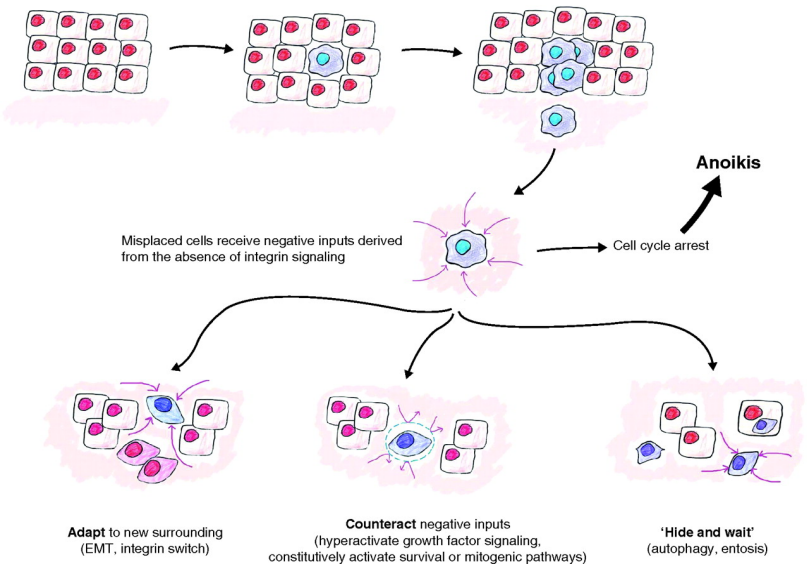


Fig 3: Anoikis in the absence of integrin (Journal of Cell Science, 2011)

2.4 Parthanatos:

"PARP-1 mediative cell death"

PARP-1: poli (ADP-Riboz) polymerase-1

Caspase is an independent cell death. It is accepted as subtype of necroptosis. For parthanos AIF is important. Core remains are comprehensible at mollecular mechanizm during mitochondrial AIF resonance; nevertheless it is prefered having a possible role of calpasin-1. AIF is a mitochondrial protein. It is important for surviving of cell. It is waved from mitochondria to the core and it is Caused to DNA fragmentation at the serially biochemical occured cell death and cell death in consequence of nuclear condensation [11]. For the wave of AIF from mitochondria, a lot of mechanizms are stimulated under the different cell death or they include caspases, calpasins and PARP-1 which are identified at experiential terms [12]. Parthanatos has an important role for cellular injury except nervous system, ischaemia, diabet, atherosclerosis and arthritis [13] (Figure 4).

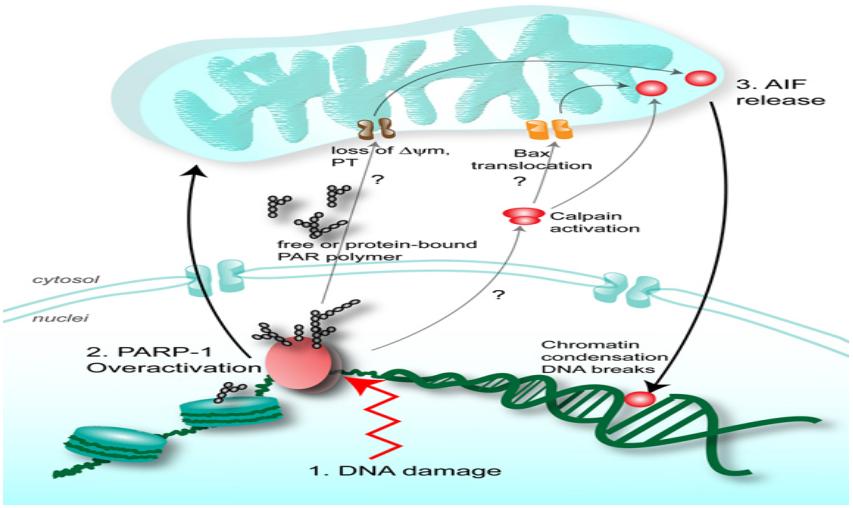


Fig. 4. PARP-1 overactivation leads to cell death. In the presence of death stimuli such as excessive DNA damage (1), PARP-1 overactivation (2) leads to the release of the death effector AIF from the mitochondria (3). The biochemical events mediating this nuclear-mitochondrial crosstalk are not completely known (Frontiers in Bioscience 2009, 14(1):1116-28).

2.5 Paraptosis:

This term is used for different programmed cell death from apopitoz as of morphological and biochemical. Paraptosis is changed on during expressing by growth factor receptor 1 like insulin at multivariete cell types. Paraptosis is characterized by cytoplasmic vacuolisation, it starts with the growth of mitochondria and endoplasmicreticulum [14]. In general, it neither replies for caspase inhibitories nor consists of caspase activation;creation of apoptotic particles or apoptotic have other morphological features. Paraptosis is identified by arbitrating with protein kinase which is activated by mitogen [15]. TNF receptors are set off by the family members TAJ / TROY and the growth factor receptor suchlike insulin. It is indeterminant that paraptosis is a cell death whether or not, which is different from others. Caspase is independent. It is similar to necrosis.

2.6 Pyroptosis:

Pyroptosis is a host cell death which is stimulated by pathogen or toxins. Pyroptosis's first definition is identified in 2000, at infected macrophages *Salmonella typhimurium* [16]. Microorganisms which work a lot is, *Pseudomonas aeruginosa*, *Shigella flexneri*. Researchers find that cas-3 does not mediate to cell death patway suchlike apoptosis but cas-1 mediates [17]. At *Shigella* macrophage death is stimulated independently from p53 however p53 is important for apoptosis [18]. It is interesting that during Salmonella infection, at the cas-1 dependent cell death dendritic cell type is identified that this form is unlimited with macrophage [19]. Cas-1 is a first caspase inflamation and a protypical member of caspase subfamily which is identified to mammals. Apical activation of caspase -1 includes protease (except cas-3) which is known as 1L-1β- converting enzyme. Like other caspases it is responsible for Division of cas-1 pro-IL-1β. Its biologically waved forms of cytokine enter pro-IL-18 and pro-IL-13 to their iner [20]. It does not have a role like classical apoptosis. In addition to this, when finished lipopolysaccaride macrophagens are exposed to pyroptosis, correlator protein ASC mediates. Forms of caspase come together with these and create supramollecular cytoplasmic complex. It is known as "pyroptosome" [21]. In this way different ways cause pyroptosis for caspase -1 activaiton. Releasing of IL-1β (this big inductive is one of the cytokine or pyrogenous) and IL-18 cause for this type of cell death and they can have a role in related to reactions of regional and systematical inflammatory [22]. Today's macrophagens are exposed to pyroptosis is not only similar to apoptosis morphologically. At the same time it has samples in relation to necrosis [23] (Figure 5).

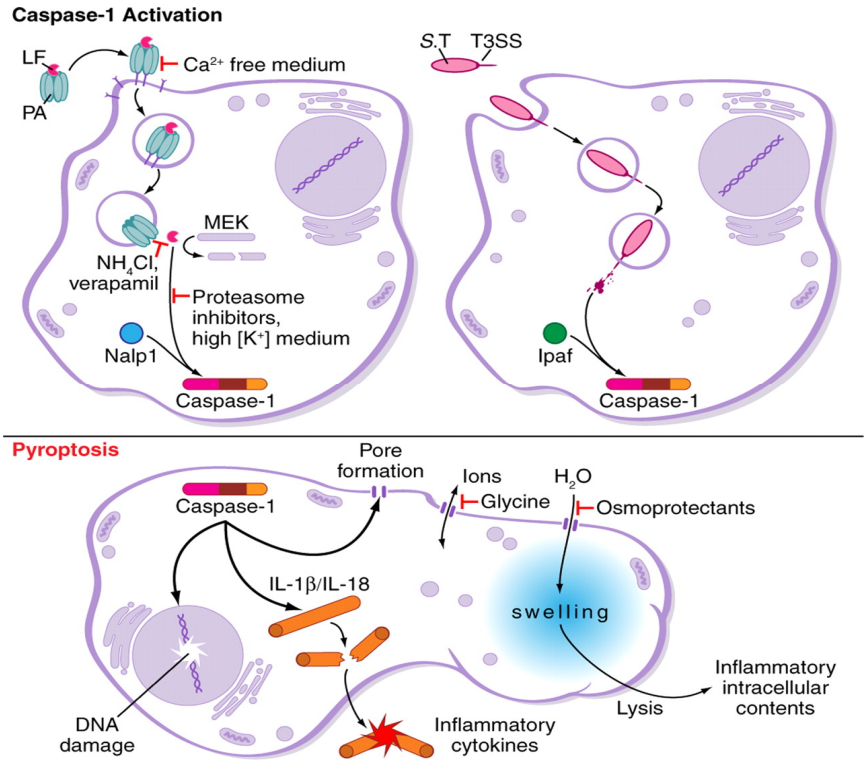


Fig 5: Lethal toxin and *Salmonella* use distinct mechanisms to elicit the common pathway of caspase-1-dependent pyroptosis. (*Upper*) The LT complex consisting of PA and LF is taken up by macrophages in a Ca2_-dependent manner. Endosome acidification, which is blocked by NH4Cl, triggers a conformational change in PA, allowing translocation of LF into the cytosol. The Ca2_ channel blocker verapamil also inhibits LF translocation. In the cytosol, LF proteolytically cleaves MEK and other substrates, after which caspase-1 activation requires proteasome activity, potassium efflux, and the inflammasome protein Nalp1. *Salmonella* infection stimulates caspase-1 by an independent pathway requiring ligand(s) delivered by the bacterial type III secretion system (T3SS) and the inflammasome protein Ipaf. (*Lower*) Caspase-1 activated by both stimuli mediates a common pathway of pyroptosis: cell death featuring DNA fragmentation, secretion of activated inflammatory cytokines, and lytic release of inflammatory intracellular contents mediated by the formation of membrane pores between 1.1 and 2.4 nm in diameter. Osmotic lysis during pyroptosis is blocked by osmoprotectants and the cytoprotective agent glycine. (Fink vd, 2008)

2.7 Entosis

Apoptotic cells are generally absorbed by phagocytes or neighbour cells. Nevertheless the alive cells are absorbed by the other cells and it is called entosis. In the cell biology it takes a part as cannibalisim [24]. It is discovered as entosis at the human's tumor and entosis activates with losing dependency on engulfs of cells. Although it is not very clear, it needs a signal called "eat me" for entosis. It is needed cadherine for entotic cell –for reaction of cell. Entosis is an unmasked way which other catabolic ways are suppressed and other points are wait for discovering. Entosis Bcl-2 or Z – VAD is inhibited by fmk and internalized cells are seen normal. Afterwards it probably gets lost with lysosomal destruction. At rare exceptions it is divided into internalized cells or released [24]. In this reason it is not easy to know that entosis is a new cell death whether or not [25] (Figure 6).

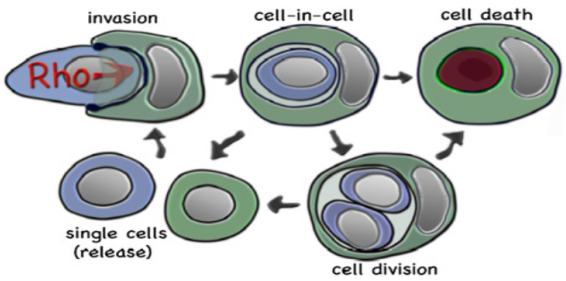


Fig 6: An illustration of entosis. A matrix-detached target cell (top left, blue) invades (arrow) into a neighboring host cell (turquoise) by a Rho-dependent contractile actomyosin forcebased mechanism, requiring E-cadherin and adherens junction formation (blue junction at the cell–cell interface). The target cell is then internalized by the host. An internalized cell can be degraded by lysosomal enzymes (the red cell), can undergo cell division inside the host, or an be released from the host. (Kindly contributed by Michael Overholtzer and Joan S. Brugge.) (Yuan ve Kroemer, 2010)

2.8 Pyronecrosis:

Necrotic cell death, related to Nalp3 and ASC, of infected macrophagens with *Salmonella flexneri* is connected with waved of HMGB – 1, cas – 1 and IL - 1β and it is called with pronecrosis [26]. Pyronecrosis is differed from pyroptosis because of requiring cas – 1 for pyroptosis. In this division RIP -1 mollecular is used. RIP -1 has a role in the natal defense system [22]. However it remains for determining that it has a role at pyroptosis and pyronecrosis whether or not.

2.9 Necroptosis:

It is also known as "programmed necrosis". Morphological characterization is that increasing in the volume of cell, swelling of organelles, plasma membrane rupture, followed by leakage of intracellular contents [27]. Necroptosis is stimulated by TNFαR, FasL and TRAIL. It connectes with a way which is similar to apoptosis. RIP1 has an important role in the kinase binding region. In this pathway activity of cool / treonin kinase is important but it is not needed for NF-κB activaiton and apoptosis [28]. Nec-1 (necrostatin; necropytosis inhibitor) is a small mollecul which has a speciality for stopping RIP-1 kinase activity and necropitosis. Under apoptosis dependent circumstances, TNFα causes that stimulant two proteins complex are formed; these are complex I and complex II a. It stimulates NF-κB activation and apoptosis. For getting strong or providing of NF-κB RIP 1 (Risk Iron – sulfur protein) TNFα connects to TNFR1 receptor that it is inductive. Other proteins and proteins and this receptor create the complex I. After that these componenets divides from TNFR1 and they can be in the RIP1 complex II a cytosol. Cytosol RIP1 consists of caspase γ and FADD. It is not clear that complex 1 transforms into complex II with signals. Alternative multivariete protein (kept together) is named "complex II b". Transforming into complex II is occured when apoptosis is lack (in particular cas-8 inhibitor is exist). Complex II b also includes RIP3. RIP1 and RIP3 are important for this complex transformation.CYLD is identified by Hitomi and colleagues in 2008 [29]. It has a mediative role in the TNFα stimulant of vital apoptosis and necropytosis (Figure 7).

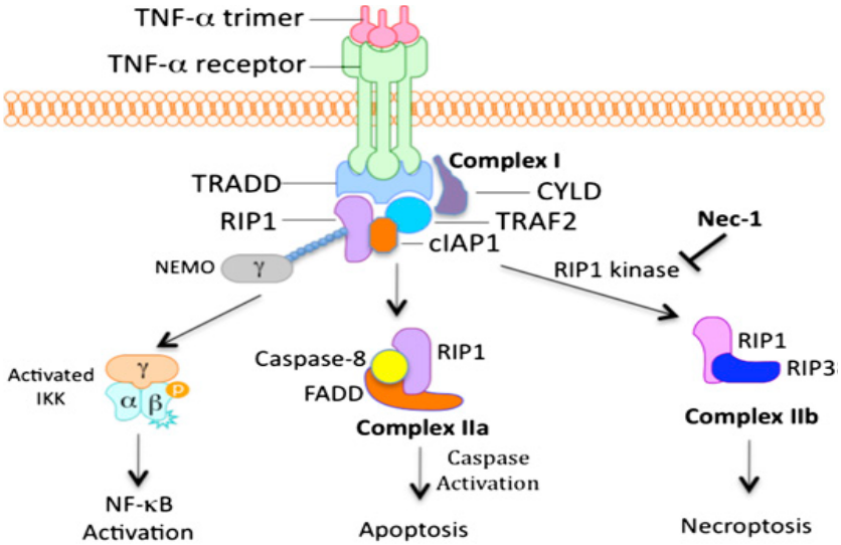


Fig 7: The signaling complexes are induced by TNFa to mediate NF-kB activation, apoptosis, and necroptosis. (Yuan ve Kroemer, 2010)

2.10 Netosis:

It is a type of cell death which is occured only in the granulocytes. In this type of cell death NETs take a part. NETs (neutrophile extracellular holder) wave eosinophils [30], mast cells [31] (except basophiles) and this reason it is identified as ETOSIS by Wartha and colleagues [32]. NETs are agents which are occured by chromatin and antimicrobial agents (elastas, cathepsin G, LL-37 and histone) waved from these cells against various stimulants [33].

NETs have features that they can keep and take off a lot of bacterias, mycose and protozoal pathogens [34, 35]. Invivo NETs are waved during cell death because of pathogen and called netosis. In specific pathological circumstances NETs are related to various tissue damage and autoimmune diseases [36]. Neutrophile performance and their function absorb microorganisims or opsonisation and break up various mollecullar with lytic enyzme [37]. Netosis caspase is an independent cell death consequently caspase is not influenced by inhibitors and necrostatine [38] (Figure 8).

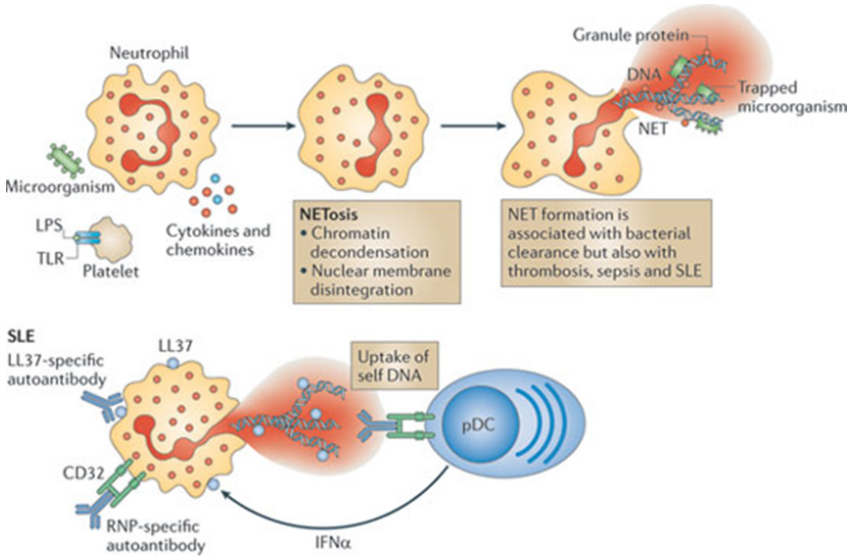


Fig. 8. Neutrophils and NET formation (Nat. Rev . 11, august ,2011)

3. Conclusion

This article is written by referring to NCDD's foreseeing types of cell death. It is clearly be seen that in the forthcoming years more types of cell death are discovered. Classification of cell death is done with foreseeing of NCCD's biochemical parameters. In this point its physiopathologic importance and signalling specificity are foreseen. Pharmacological inhibitors and activators are used. In addition to this between the different types of death determine and type of cell death is programmed whether or not.

For understnading mollecular mechanisms which is controlled by physiological added to cell deaths and pathologic operations and also with discovering new genes and their products provide a basis to developing new models of diagnosis and treatment in the future.

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