Programirana smrt stanice-povijesni prikaz; jedna je apoptoza?

Faruk Skenderi1, Monika Ulamec2

1Klinika za patologiju i citologiju, Univerzitetski klinički centar Sarajevo, Sarajevo, Bosna i Hercegovina

2Klinički zavod za patologijuLjudevit Jurak, Klinički bolnički centar Sestre milosrdnice, Zagreb, Hrvatska, Medicinski fakultet, Sveučilište u Zagrebu, Hrvatska

Regulirana stanična smrt je kontrolirani proces koji se može pokrenuti u fiziološkim i patološkim procesima. Poremećaj regulacije stanične smrti upleten je u nastanak mnogih patoloških stanja, poremećaje razvoja, imunološke poremećaje te neurodegenerativne bolesti i tumore.

Smrt stanice opisana je još 1842.g. (C Vogt) kada su u embriju žabe uočene stanice koje umiru. Flemming je 1885.g. opisao spontanu staničnu smrt (koju je nazvao kromatoliza) kao pojavu koja se razlikuje od nekroze. Njemac Graper objavio je rezultate o fiziološkoj eliminaciji stanice koja stoji nasuprot procesu mitoze, ali tada nije privukao pažnju suvremenika. Glucksman, Kerr, Locksin i Williams dali su detaljne opise mehanizama programirane smrti, još 1951. i 1965. g. sugerirana su dva morfološka oblika: oblik degenerativne smrti-nekroza i nedegenerativne- nekroza skupljanja („srinkage necrosis“). Druga je karakterizirana pojedinačnim stanicama ili manjim nakupinama stanica gdje se jezgra i stanica smanjuju i „suše“, jezgra ostaje održana, nema upalnog odgovora.

Kerr (1972.g.) i Wyllie (1980.g.) objašnjavaju koncept apoptoze- aktivno programirana i kontrolirana stanična smrt suprotna mitozi, a koja regulira broj stanica te može biti aktivirana fiziološkim ili patološkim stimulusima. Otvaranjem novih mogućnosti i upotrebom novih molekularnih metoda analize, dolazi do identifikacije specifičnih gena povezanih s apoptozom te proteina upletenih u mehanizam apoptoze.

 Sve donedavno programirana smrt stanice korištena je kao sinonim za apoptozu, no ipak je uočeno (2007.g.) da se naziv odnosi na više genetski određenih i reguliranih procesa koji rezultiraju morfološki prepoznatljivim oblicima stanične smrti; apoptoza, autofagija te nekroptoza. Obzirom na razvoj različitih teorija i naziva za proces stanične smrti, oformljen je odbor za određivanje nomenklature te su 2005.g. predloženi kriteriji i definicije koje se odnose na staničnu smrt. Tada se klasifikacija temeljila isključivo na morfološkim kriterijima. S razvojem i otkrivanjem različitih molekularnih mehanizama i puteva dane su preporuke za točne molekularne definicije i precizne metode detekcije i kvantifikacije stanične smrti, a koje su bile manje subjektivne, s boljom reproducibilnošću rezultata istraživanja.

Preporuke od 2014.g. donose opis dva osnovna tipa stanične smrti- naprasna stanična smrt („accidental cell death“-ACD) i regulirana stanična smrt („regulated cell death“-RCD). ACD nastaje u nekontroliranim uvjetima, zbog ekstremnih fizičkih, kemijskih ili mehaničkih stimulusa, a slijedi dezintegracija stanice. RCD je genski regulirana, može nastupiti u patološkim ili fiziološkim uvjetima, a ako se radi o fiziološkim procesima tada se zove programirana smrt stanice. Mnogi molekularni mehanizmi sudjeluju u opisanim procesima, ali ukoliko je blokiran jedan put stanica može iskoristiti drugi, alternativni put.

 Procesi koji su nekada opisivani pod jednim imenom sada su razdijeljeni, ovisno o mehanizmima koji ih pokreću te putevima kojima se koriste, npr.piroptoza, NET-oza (stanična smrt imunološki aktivnih stanica tijekom upalne reakcije zbog djelovanja na mikrobe) ili entoza („napad“ jedne stanice na citoplazmu druge stanice, a zbog gubitka međustaničnih veza).

Mnoge spoznaje su objavljene u polju istraživanja mehanizama stanične smrti, a čiji poremećaji dovode do različitih patoloških stanja. Terapeutske mogućnosti koje su povezane s regulacijom i utjecajem na različite mehanizme stanične smrti mogu imati široke implikacije na različite bolesti. Unatoč tome, dijagnostičke mogućnosti upotrebe različitih proteina i gena regulacije stanične smrti još su uvjek ograničene.

Literatura:

1. Šarčević B. Apoptosis in tumors. Acta Med Croatica. 2009;63:43-47.
2. Kroemer G, Galluzzi L, Vandenabeele T i sur. Classification of cell death: recommendations of the Nomenclature Committee on Cell Death 2009. Cell Death Differ.2009;16:3–11.
3. Galluzzi L, Vitale I, Abrams JM i sur. Molecular definitions of cell death subroutines: recommendations of the Nomenclature Committee on Cell Death 2012. Cell Death Differ. 2012;19:107–120.
4. Skenderi F, Vranić S, Damjanov I. Regulated cell death in diagnostic histopathology. Int. J. Dev. Biol. 2015; 59: 149-158.

Programmed cell death-historical review; is there one apoptosis?

Faruk Skenderi1, Monika Ulamec2

1Department of Pathology, Clinical Center, University of Sarajevo, Sarajevo, Bosnia and Herzegovina

2Ljudevit Jurak University Department of Pathology, Sestre milosrdnice University Hospital, Zagreb, Croatia, School of Medicine, University of Zagreb, Zagreb, Croatia

Regulated cell death is a programmed process that is initiated in physiological and pathological processes. Deregulation of cell death is involved in the development of many pathological conditions, disorders of development, immunological disorders and neurodegenerative diseases and tumors.

Cell death was described in 1842. (C. Vogt) when dying cells were observed in frog embryos. In1885. Flemming described a spontaneous cell death (named cromatolysis) as a phenomenon different from necrosis. Gräper pointed out that process of the physiological cell elimination is opposite to the mitotic trial, but his observations didn’t attract the attention. Glucksman, Kerr, Locksin and Williams gave detailed descriptions of programmed cell death mechanisms and 1951 and 1965.y. suggested two of morphological forms: a form of degenerative death-necrosis and nondegenerative -shrinkage necrosis. The second is characterized by individual cells or small clusters of cells where the nucleus and cell is shrinking and nucleus is reduced, there is no inflammatory response.

Apoptosis was defined by Kerr (in 1972) and Wyllie (in 1980) as an active, programmed and controlled cell deletion mechanism, which plays a complementary but opposite role to mitosis in regulation of cell population number, and can be triggered by both physiological and pathological stimuli.

With the advent of new possibilities and the use of new molecular methods in analysis, identification of specific genes associated with apoptosis and proteins involved in the mechanism of apoptosis emerged.

Until recently programmed cell death was used as a synonym for apoptosis, but it became evident that regulated cell death may not refer onlly to apoptosis, but rather to a number of genetically regulated processes, resulting in one of the morphologically well-defined cell death types. The Nomenclature Committee on Cell Death (NCCD) was formed in 2005 to propose unified criteria for the definition of cell death and different cell death morphologies. The classification was based solely on morphological criteria but with the development and detection of different molecular mechanisms and pathways the recommendations for exact molecular definition and accurate methods of detection and quantification on cell death were given. It was less subjective, with better reproducibility on research results.

Recommendations from 2014 brought description of two basic types of cell death- accidental cell death (ACD) and regulated cell death (RCD). ACD occurs in uncontrolled conditions, due to extreme physical, chemical or mechanical stimuli, followed by the disintegration of cells. RCD is regulated by genes; it may start in pathological or physiological conditions, and then it is called physiological programmed cell death. Many molecular mechanisms are involved in the described processes, but if one pathway is blocked cells can use alternative.

Processes that were once described under one name are now divided, depending on the mechanisms that drive them and the pathways they use, e.g. pyroptosis, NETosis (cell death of immunologically active cells during inflammatory reactions due to the effect on microbes) or entosis (one cell attacks the cytoplasm of other cell with the loss of intercellular junctions).
Several papers have been published in the field to investigate the mechanisms of cell death and disorders which lead to various pathological conditions. Therapeutic options that are related to the regulation of cell death which influence different mechanisms of cell death may have broad implications for a variety of diseases. Nevertheless, the diagnostic possibilities of using different proteins and genes regulating cell death are still quite limited.

References:

1. Šarčević B. Apoptosis in tumors. Acta Med Croatica. 2009;63:43-47.
2. Kroemer G, Galluzzi L, Vandenabeele T et al. Classification of cell death: recommendations of the Nomenclature Committee on Cell Death 2009. Cell Death Differ.2009;16:3–11.
3. Galluzzi L, Vitale I, Abrams JM et al. Molecular definitions of cell death subroutines: recommendations of the Nomenclature Committee on Cell Death 2012. Cell Death Differ. 2012;19:107–120.
4. Skenderi F, Vranić S, Damjanov I. Regulated cell death in diagnostic histopathology. Int. J. Dev. Biol. 2015; 59: 149-158.