Seminars in Cell & Developmental Biology 68 (2017) 85–90

Contents lists available at ScienceDirect

Seminars in Cell & Developmental Biology

journal homepage: www.elsevier.com/locate/semcdb

Review

# Strategic disruption of nuclear pores structure, integrity and barrier for nuclear apoptosis

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ARTICLE INFO

*Article history:*
Received 27 June 2017
Accepted 3 July 2017
Available online 12 July 2017

*Keywords:*
Apotosis
Nuclear pore complexes
Nuclear envelope
Nucleocytoplasmic transport
Atomic force microscopy

ABSTRACT

Apoptosis is a programmed cell death playing key roles in physiology and pathophysiology of multi cellular organisms. Its nuclear manifestation requires transmission of the death signals across the nuclear pore complexes (NPCs). In strategic sequential steps apoptotic factors disrupt NPCs structure, integrity and barrier ultimately leading to nuclear breakdown. The present review reflects on these steps.



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## 1. Physiological, pathophysiological and medical relevance of apoptosis

Cells are generally anchored together in tissues. A rotten apple spoils the barrel and by analogy to this idiom, a cell that has come to harm in a tissue may spoil the neighbouring cells unless it is removed. Unlike the rotten apple, the harmed cell sacrifices itself voluntarily in a tightly controlled way to protect its neighbourhood. This selfless act of an individual ensures the safety of the collective. The distinctive cell suicide process termed apoptosis is of fundamental physiological importance. While a pathological loss of cells, for instance as result of injuries, is undesired, apoptosis confers key advantages during the life cycle of multicellular organisms. Essentially every animal cell is capable of undergoing apoptosis if it comes to serious harm or if is not desired any more [1].

The fundamental physiological importance of apoptosis is underpinned by its critical roles in development and homeostasis. It is required to shape up the desired structures much like sculpting. For instance, the differentiation of fingers and toes in a human embryo is mediated by apoptosis. Cells between fingers and toes commit apoptosis and the consequence thereof is that digits are separate. Apoptosis regulates the clearance of cells during development as well as under pathophysiological circumstances for the ultimate benefit of the organism [1]. The number of cells in the adult organism is kept relatively constant by a balance between apoptosis and cell division. Malfunctioning or diseased cells must be removed and replaced but at the same time proliferation must be kept in check [2]. As a consequence of the stringent quality control-based maintenance/proliferation or clearance of cells, apoptosis restricts the accumulation of harmful and potentially dangerous cells such as self-reactive lymphocytes, virus-infected

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http://dx.doi.org/10.1016/j.semcdb.2017.07.002
1084-9521/

cells, and tumor cells [1,3–7]. This balance between cell death and proliferation is kept under control throughout the adult life. Hence, apoptosis takes centre stage in diverse physiological process throughout life including. On the other hand, evasion of apoptosis by malignant cells or imbalance in apoptosis levels gives rise to the pathogenesis of a wide range of diseases. For instance, increased levels of apoptosis are closely associated with AIDS, diverse neurodegenerative diseases, myopathies, neurodegenerative diseases including Alzheimer and Parkinson and amyotrophic lateral sclerosis, ischaemic injuries after myocardial infarction, stroke and reperfusion, as well as autoimmune diseases [2,4]. Decreased or inhibited apoptosis is a feature of diverse cancer, autoimmune disorders such as systemic lupus erythematosus, and some viral infections. Owing to the broad pathophysiological implications, the urgency of refining our incomplete knowledge of apoptosis is blatant. Despite the substantial knowledge acquired so far, there are many open questions yet and the investigation of apoptosis must carry on in full swing. As a matter of fact, the justified hopes are that apoptosis research will set the stage for the design of new potent drugs to treat severe, often deadly diseases spread worldwide [8].

## 2. Steps of the apoptosis process

Despite the complexity and diversity of the highly complex and tightly orchestrated process of apoptosis, the basic mechanism is strongly conserved throughout animal evolution, from C. elegans to Drosophila to humans [1,3,9]. Therefore, the investigation of apoptosis in simple model organisms which can be genetically modified offers an attractive approach to understand the complexity of this process and its implications for physiology and pathophysiology. Striking progress has been made concerning our understanding of apoptosis over the last decades. The general agreement is that this sophisticated multi-step process is set into operation by the activation of an intrinsic programme constitutively expressed in the majority of animal cells, and that the essential components needed for the execution have been conserved from worms to insects to humans [4]. Apoptotic cells are easily singled out from the crowd by phagocytes. They are identified as suspiciously different from their intact and inconspicuous neighbouring cells and are rapidly targeted for clearance. Interestingly, phagocytes are normally recruited for the destruction of foreign bodies but apoptotic are no strangers [10–13]. Obviously, the dying cells transmit specific signals raising the alarm of the ready-for-action phagocytes which rush to engulf and break them down to recycle their contents [11]. While stimuli promoting apoptosis are diverse, signalling and execution follow a strict plan [8,11,14,15] giving rise to activation of family of cysteine proteases termed caspases, which are generally kept in check as inactive precursor enzymes in healthy cells. Apoptosis is primarily executed, but not exclusively, by initiator and effector caspases [11]. Typically, initiator caspases are set into operation by specific apoptosis stimuli while effector caspases are engaged in implementing the tightly regulated destruction of the cell [11]. Three main apoptosis routes are known to activate caspases and they all share the release of cytochrome c from mitochondria and the initiation of caspase-3, caspase-6 and caspase-7 [11]. These major effector caspases account for much of the proteolytic activities during apoptosis [11]. The ultimate outcome is a destruction of the doomed cell, which manifests in sequential events including cell shrinkage, mitochondrial fission, blebbing of the plasma membrane, condensation of the nucleus, fragmentation of the nucleus and the DNA and the generation of apoptotic bodies [10,11,16,17]. These hallmarks are paralleled by substantial changes in nuclear envelope and nuclear pores structure, function, integrity and barrier function, critical for the manifestation of nuclear apoptosis [18–22].

## 3. Mechanical destabilisation of the apoptotic nuclear envelope sets the stage for the collapse of the cell nucleus

Condensation of the nucleus and its breakdown into small fragments is an unmistakable feature of apoptosis requiring a very strategic course of events. Taylor et al. [11] likened the collapse of the cell nucleus during apoptosis to a thoroughly planned demolition of a large old building by a squad and this analogy hits the mark. In fact, the building must be thought of as being standing in the middle of a crowded district and therefore the demolition must be strictly limited to the target building. Moreover, the set explosives must crash down the building like a house of cards and flying debris must not reach the neighbouring buildings. We have to bear in mind that large areas in a district is evacuated prior to

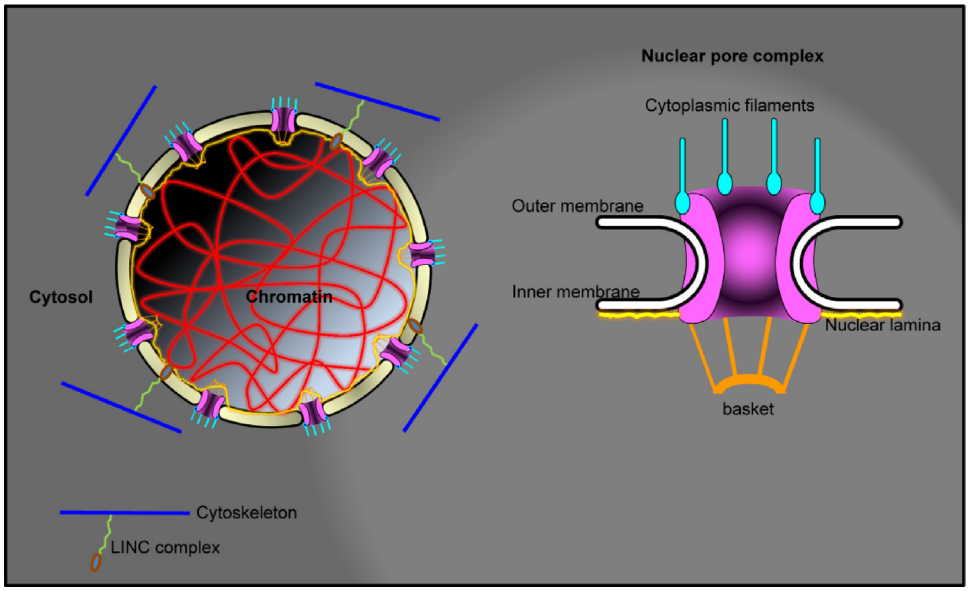


**Fig. 1.** Schematics of the biophysical bonds between the nucleoplasm and the cytoplasm, and of the nuclear pore complex. The cytoskeleton is regularly interconnected with the nuclear lamina through LINC complexes. These bonds, in turn, are associated with chromatin sites.