Role of Apoptosis in Neonatal and Pediatric Sepsis

Essay

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قالُوا سُبْحَانَكَ لاَ عِلْمَ لَنَا إِلاَّ مَا عَلَّمْتَنَا إِنَّكَ أَنتَ الْعَلِيمُ الْحَكِيمُ

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Samer Saleh Abd Elnaaem

Contents

List of Abbreviations

AIF	:	Apoptosis Inducing Factor
ALPS	:	Autoimmune lymphoproliferative syndrome
Apaf	:	Apoptotic protease activating factor
ARDS	:	Acute respiratory distress syndrome
CAD	:	Caspase-activated DNAse
CED	:	Cell death abnormal
CLP	:	Cecal ligation and puncture
COX	:	Cyclooxygenase
CRP	:	C-reactive protein
DAMP	:	Damage- associated molecular pattern
DC	:	Dendritic cells
DD	:	Death domain
DED	:	Death effector domain
DISC	:	Death-inducing signalling complex
DR	:	Death receptors
DS	:	Down Syndrome
ER	:	Endoplasmic reticulum
ES	:	Embryonic stem
ESL-١	:	E-selectin ligand-١
FADD	:	Fas-associated death domain
FLIP	:	Fas-associated death domain- like IL-١-converting enzyme- inhibitory protein
Gas٦	:	Growth arrest-specific ٦
GM-CSF	:	Granulocyte macrophage colony stimulating factor
HC	:	Heavy chain
HMGB١	:	High-mobility group box ١
HSPs	:	Heat shock proteins
ICAD	:	Inhibitors of caspase activated DNAse
IELs	:	Intestinal intraepithelial lymphocytes
IFN-gamma	:	Interferon-gamma
Ig	:	Immunoglobulin

List of Abbreviations (Cont.)

IL	:	Interleukin
IL-١	:	Interleukin
iNOS	:	Inducible nitric oxide synthase
LC	:	Light chain
LPS	:	Lipopolysaccharide
LTA	:	Lipoteichoic acid
MAPK١	:	Mitogen activated protein kinase ١
Mfge٨	:	Milk fat globule-epidermal growth factor-٨
MHC	:	Major histo-compatibility complex molecules
MOMP	:	Mitochondrial outer membrane permeabilization
NF-κB	:	Nuclear factor kappa- light-chain-enhancer of activated B Cells
NK	:	Natural killer
NO	:	Nitric oxide
PAF	:	Platelet Activating Factor
PAMPs	:	Pathogen-associated molecular patterns
PARP-١	:	Poly (ADP-ribose) polymerase-١
PCD	:	Programmed cell death
PCT	:	Procalcitonin
PS	:	Phosphatidylserine
Ptx٣	:	Pentraxin ٣
ROIs	:	Reactive oxygen intermediates
ROS	:	Reactive oxygen species
SCID	:	Severe combined immunodeficiency
SIRS	:	Systemic inflammatory response syndrome
TCR	:	T cell receptor
Tim	:	T-cell immunoglobulin domains and mucin domain
TLRs	:	Toll-like receptors
TNF-α	:	Tumor necrosis factor-α
TRAIL	:	TNF-related apoptosis-inducing ligand

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Introduction

Sepsis is defined as Systemic illness caused by microbial invasion of normally sterile parts of the body ***(Andrew Lever, ٢٠٠٧).***

Sepsis is a leading cause of death in infants and children, with >٤٢،٠٠٠ cases of severe sepsis annually in the United States and millions worldwide (***Watson,*** ٢٠٠٥)

The common causes of sepsis are (gram-positive bacteria, gram-negative bacteria, mixed bacteria, fungi, other, and unknown microbial etiology) ***(Steven M. Opal, ٢٠٠٣)*** for example : gram-positive sepsis due to [*Streptococcus pneumoniae*, *Staphylococcus aureus*, viridans streptococci, etc….] and gram-negative sepsis caused by [*Neisseria meningitidis*, *Escherichia coli*, *Proteus mirabilis*, etc….] ***(Holub, ٢٠٠٣).***

The pathophysiology of sepsis arises largely from the response of the host's innate immune system, under the influence of genetic factors. The most popular theory is that the inflammatory process loses its autoregulatory capacity; however, microcirculatory dysregulation and apoptosis may also be important, and a new paradigm posits a complex nonlinear system ***(Despond, ٢٠٠١).***

There are many theories and mediators that contribute to sepsis: Mediators of the pathogenesis of sepsis include tumor necrosis factor α (TNF-α), interleukins, platelet activating factor, leukotrienes, thromboxane $A_٢$, and activators of the complement cascade ***(Roger and Bone, ١٩٩١).***

Some mediators are considerd as early indicators as Neutrophil CD٦٤ and IL-٨ which are increased with severe sepsis ***(Olga Livaditi, ٢٠٠٦)***

Other agents that may participate in the sepsis cascade include adhesion molecules, kinins, thrombin, myocardial depressant substance, β-endorphin, and heat shock proteins. Endothelium-derived relaxing factor and endothelin-١ are released from the endothelium and seem to exert a regulatory effect, counterbalancing each other.

So in total it is more likely that sepsis is related to the state of activation of the target cell, the nearby presence of other mediators, and the ability of the target cell to release other mediators. Also important is the downregulation or negative feedback of these mediators or the generation of natural inflammation inhibitors, such as interleukin-٤ and interleukin-٨.***(Roger and Bone,١٩٩١).***

The pathogenesis of severe sepsis is characterized by organ damage and accumulation of apoptotic lymphocytes in the spleen, thymus, and other organs ***(Irmeli Nupponen) .***

Apoptosis is an evolutionarily conserved, energy-dependent mode of cell death requiring the initiation and regulation of complex genetic programs ***(Mahidhara, ٢٠٠٠).***

Apoptosis of circulating neutrophils from patients with clinical sepsis is profoundly suppressed, through a mechanism that involves activation of nuclear factor-κB that is associated with reduced activity of caspases-٩ and -٣ and maintenance of mitochondrial transmembrane potential and that differs in important respects from the inhibitory effects seen following the exposure of healthy neutrophils to inflammatory stimuli ***(Taneja, ٢٠٠٤).***

During sepsis, there is extensive apoptotic death of lymphocytes and gastrointestinal epithelial cells. The extensive apoptotic death of lymphocytes is likely an important cause of the profound immunosuppression that is a hallmark of patients with sepsis. The apoptosis of gastrointestinal epithelial cells

may compromise the integrity of the bowel wall, resulting in translocation of bacteria or endotoxins into the systemic circulation, Blocking lymphocyte apoptosis improves survival in sepsis ***(Richard and Hotchkiss ٢٠٠٥).***

Most deaths from sepsis are actually the result of a substantially impaired immune response that is due to extensive death of immune effector cells. Rectification of this apoptotic-inflammatory imbalance using modulators of caspases and other components of the cell-death pathway have shown striking efficacy in stringent animal models of sepsis, indicating an entirely novel path forward for the clinical treatment of human sepsis. ***(Richard and Hotchkiss, ٢٠٠٦).***

Aim of the Work

Revealing the role of apoptosis in organizing the immune system response to various infections agents and it's on the process of sepsis and septic shock aiming at providing further studies and applying early diagnostic markers and treatment strategies.

Chapter (١)

Apoptosis

Introduction:

Apoptosis is defined for the first time as an event reminiscent of the falling of leaves from trees ***(Kerr et al., ١٩٧٢).***

Apoptosis, which is also referred to as programmed cell death, is an active, energy dependent, well-defined process whereby cells carry out suicide.

Apoptosis is crucial during embryonic and fetal tissue remodeling to maintain a balance between organized cell growth and death and it is responsible for the removal of interdigital webs, about ٥٠% of excess neurons, and interstitial lung fibroblasts after lung alveolarization.

The human body contains about $١٠^{١٤}$ cells, each of which is able to initiate apoptosis ***(Hotchkiss et al., ٢٠٠٦).***

Every day, there are about ٦٠×١٠^{٩} newly developing cells, whereas old ones are removed by programmed cell death and other processes.

In the adult human organism, apoptosis plays an important role in the elimination of damaged, non-functional cells and is also a key factor during oncogenesis.

Apoptosis should normally occur in mutated cells and eliminate potential tumor cells. ***(Hengartner, ٢٠٠٠)***

Events during Apoptosis

Programmed cell death is characterized by sequential changes, including:

- Initial cell-volume reduction (whereas intracellular organelles as well as intracellular metabolism remain intact),
- Shrinkage of the nucleus, chromatin condensation (pyknosis),
- DNA fragmentation, formation of nuclear fragments (apoptotic bodies)
- Dynamic plasma membrane blebbing (zeiosis)

These morphological features represent a late/ terminal stage of apoptosis.

Another important biochemical change and an early event is the exposure of phosphatidylserine on the outside of the cell membrane, assigning the cell for phagocytosis by macrophages ***(Perl et al., ٢٠٠٥).***

This mechanism forms the basis for selective organized elimination of cells, preventing a local inflammation of the surrounding tissue ***(Hengartner ٢٠٠٠).***

In apoptosis, potential pro-inflammatory molecules become compartmentalized so that there is no concurrent inflammatory response.
There are many inducers of apoptosis, including:

- Steroids
- Cytokines such as:
  ١. Tumor necrosis factor (TNF)-α
  ٢. Interleukin (IL)-١
  ٣. IL-٦
  ٤. FasL
  ٥. Heat shock proteins (HSPs)
  ٦. Oxygen free radicals
  ٧. Nitric oxide (NO)
  ٨. FasL-expressing cytotoxic T lymphocytes

(Hengartner, ٢٠٠٠)

Forms of cell death:

Cells can die in two ways:

- By damaging their cell membrane and then undergoing necrosis

Or

- By shrinking and blebbing the intact cell membrane, which leads to apoptosis

١. ***Accidental necrosis*** (in Greek=death),

Necrosis is a pathologic form of non-programmed and energy independent cell death.

In response to cell damage / death that follows infection, it is important to rouse inflammatory reactions that can bring about humoral and cellular defense mechanisms able to handle the infective entity and at the same time restore the proper architecture and function of the damaged tissue ***(Green et al., ٢٠٠٩)***

Necrosis characterized by:

- Rapid loss of cell viability
- Cell swelling
- Loss of membrane integrity
- Induction of an inflammatory response through the release of cytoplasmic contents including proteases, toxic proteins and oxidizing molecules.

(Kerr et al., ١٩٧٢; Hirsch, et al., ١٩٩٧)

Interactions between necrotic cell and phagocytes result in a strong pro-inflammatory reaction, possibly mediated by the activation of nuclear factor kappa- light-chain-enhancer of activated B cells (NF-κB) in macrophages in a toll-like receptor (TLR)-dependent way.***(Li et al., ٢٠٠١)***