Apoptosis- **some new information**

For PG Sem I

by

Dr. Srikanta Guria

Apoptotic Cell Clearance and Apoptotic Blebbing

What is Apoptotic cell clearance?

Apoptotic cell clearance facilitates the removal of aged, damaged, infected or dangerous cells and is a vital process in the development and homeostasis of multicellular organisms.

Apoptotic cells develop dramatic morphological changes including contraction, membrane blebbing and apoptotic body formation, which are among the first and most readily identifiable features of cellular suicide.

What is Apoptotic Blebbing?

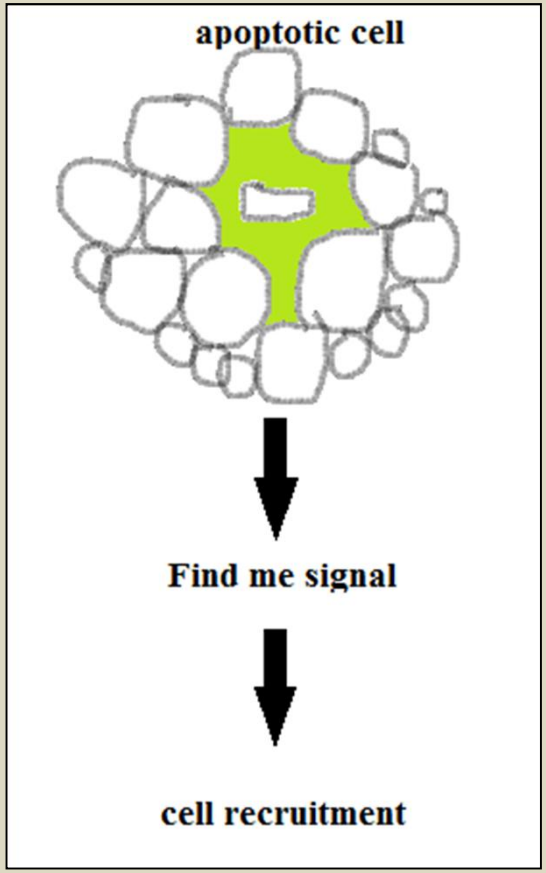
Blebs are balloon-like protrusive blisters formed on plasma membrane of apoptotic cells.

The formation of apoptotic blebs:

The formation of apoptotic blebs is a physical process that results from actomyosin mediated cellular contraction.

Apoptotic Cell Recognition and clearance

Programmed cell death, or apoptosis, is vital for the removal of problematic or unnecessary cells in multicellular organisms. **There are several phases of phagocytic clearance of apoptotic cells:**



(1) Find-me, characterized by the release of soluble signals that attract macrophages to the dying cell

(2) Eat-me, in which a phagocyte becomes stimulated by engaging with signals expressed on the apoptotic cell membrane. eg. PS (phosphatidylserine) externalization

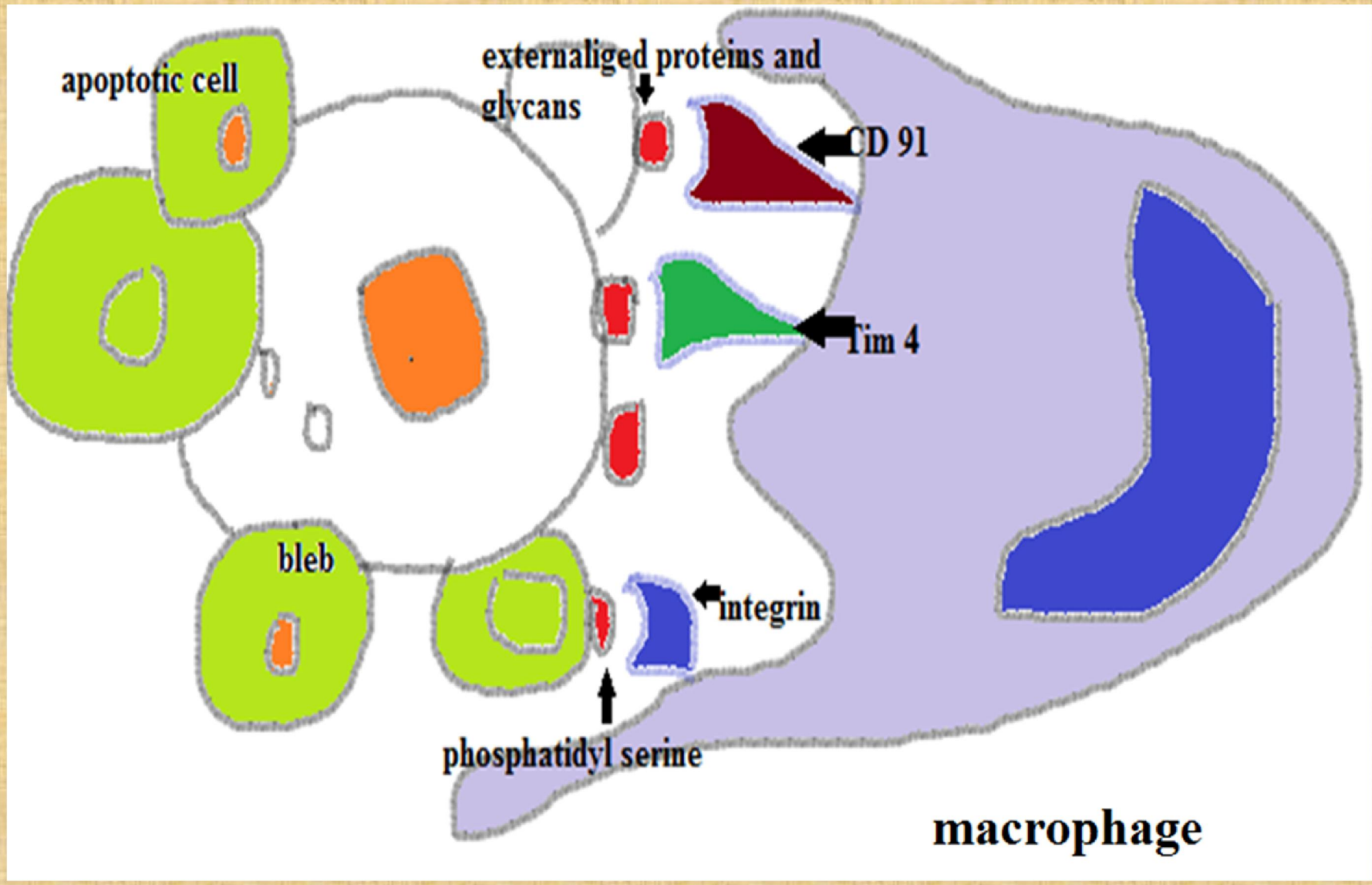
(3) Engulfment, a series of cytoskeletal modifications in the phagocyte enabling it to take up the dead cell

(4) Processing, digestion of the cellular remains through lysosomal degradation.

Eat me?

The implications of these studies are two-fold: firstly, apoptotic blebbing directly influences efferocytosis; and secondly, PS (phosphatidylserine) externalization may be a mechanism linking blebbing and phagocytosis.

In fact, microscopic analysis revealed that apoptotic blebs become highly enriched for the externalized phospholipids. Thus, it appears that apoptotic blebs serve as focal points for accumulation of externalized PS, which is then recognized by macrophages to trigger engulfment.


apoptotic cell
externaliged proteins and
glycans
CD 91
Tim 4
bleb
integrin
phosphatidyl serine
macrophage

Phagocyte chemotaxis to apoptotic bodies – a role for transglutaminase-2 ?

- As cells die by apoptosis they undergo dramatic surface changes that include the generation and release of membrane blebs known as apoptotic bodies.

- Failure to clear apoptotic cells can result in cell lysis and subsequent autoimmunity and inflammation. Effective clearance of apoptotic cells by professional phagocytes (e.g. macrophages, MØ) requires recognition and removal of apoptotic rather than viable cells, a process dependent on so called **"eat me"** signals exposed on the apoptotic cell and phagocyte receptors including innate immune receptors.

- However prior to this, professional phagocytes must migrate to sites of apoptosis along a chemotactic gradient of **"find me"** signals - factors which enhance the migration of phagocytes to sites of apoptosis.
- Transglutaminase (TG)-2, a multi-functional enzyme is released from dying cells in apoptotic bodies which diffuse from apoptotic cells to promote TG-2-dependent attraction of phagocytes.

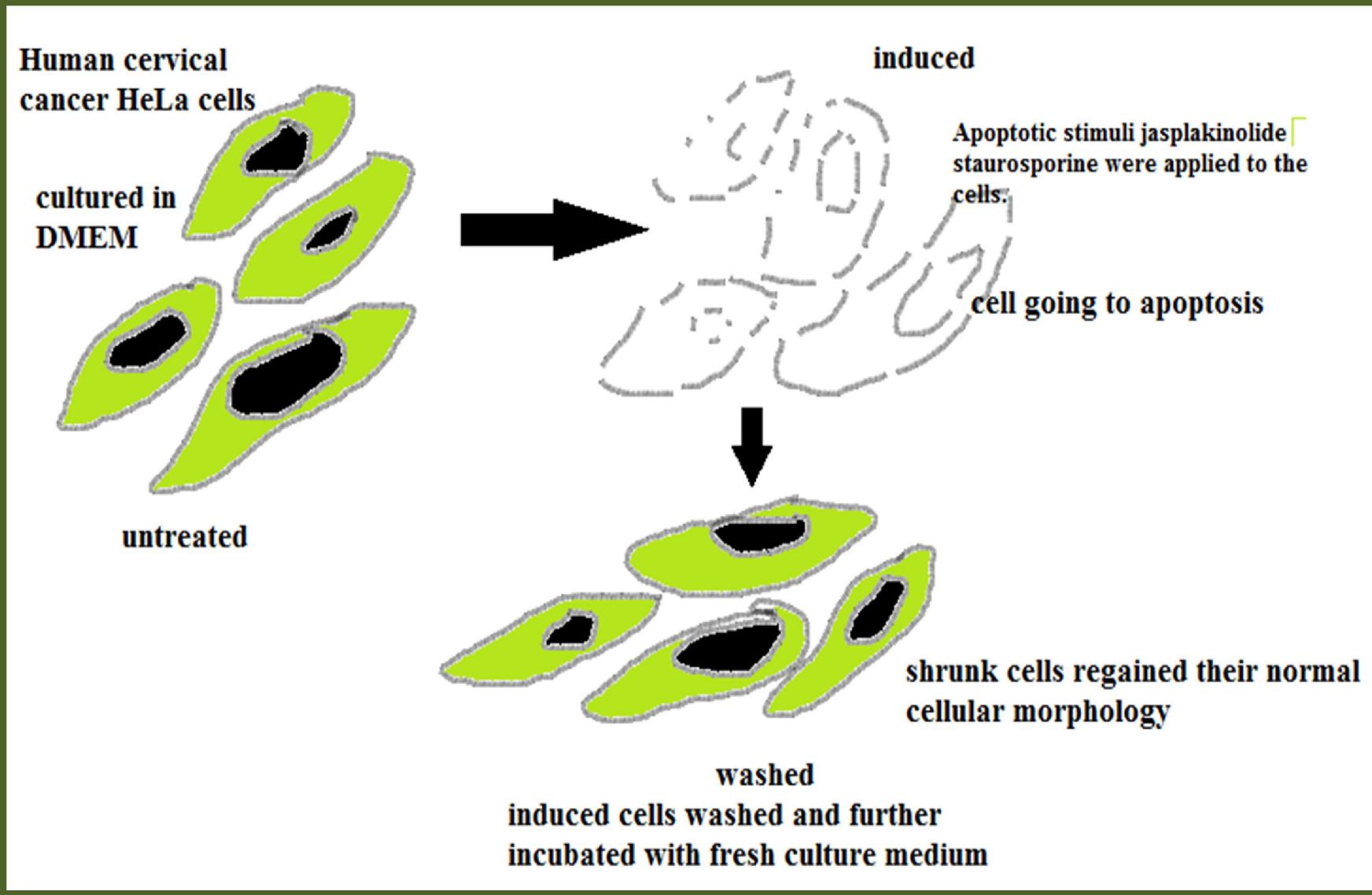
N.B-Inhibition of TG-2 enzyme activity reduces phagocyte recruitment to apoptotic bodies. This may suggest a role for TG-2 in generating a "find-me signal" associated with apoptotic bodies.

Reversibility of apoptosis in cancer cells

Chemotherapy is one of the major cancer treatments by promoting cancer cells into apoptosis (Johnstone et al, 2002; Attardi, 2005; Liet al, 2008).

Accumulating studies reported that cancers initially retreated in response to chemotherapy, but returned during repeated courses of treatment (Norton and Simon, 1977; Stephens and Peacock, 1977; Davis and Tannock, 2000; Wu and Tannock, 2003; Kim and Tannock, 2005).

Although the mechanisms of the cancer recurrence are not well understood, it is generally believed that repopulation of surviving cancer cells during the intervals between treatments is an important cause of the treatment failure (Kim and Tannock, 2005).


Human cervical cancer HeLa cells
cultured in DMEM
untreated
induced
Apoptotic stimuli jasplakinolide staurosporine were applied to the cells.
cell going to apoptosis
shrunk cells regained their normal cellular morphology
washed
induced cells washed and further incubated with fresh culture medium

cancer cells could survive after initiation of apoptosis induced by different stimuli, and the reversibility of apoptosis was observed in various cancer cell lines

thereby revealing an unexpected potential escape mechanism of cancer cells from chemotherapy

THANK YOU