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An Atomic Perspective on Apoptosis of Cancer Cells

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ABSTRACT
Most of the studies on Cancer have focused on chemical and biological interactions at molecular level. However, the living cells are made up of atoms which are the smallest particles of an element that retains its chemical properties. In a normal human body, apoptosis, is vital for normal cell turnover. Inhibition of apoptosis results in initiation and progression of Cancer. While there are different pathways and causes of cancer as well as mechanisms of tumour development, this paper considers a common pathway and mechanism and presents a theorical perspective on atomic level interactions within cells to suggests ways to maintain appropriate apoptosis (neither too little nor too much) to maintain normal modulation of life and death of a cell for maintaining a healthy human body.
Keywords: Cancer, Apoptosis, Atomic level interactions inside the cell

I. INTRODUCTION

Ashes to ashes and dust to dust – so true of the human body. Ninety nine percent of the human body is comprised of four key elements – Hydrogen, Carbon, Oxygen and Nitrogen. The elements were originally created during the big bang and the burning of stars and form the elemental components of molecules that make the cells inside the human body. While the cells inside the human body regenerate, the particles that make up those cells continue to exist. The protons and neutrons inside the atom's nucleus are each made of three quarks and these quarks are held together by gluons, the carriers of strong nuclear force. Most of the mass of the protons comes from quantum chromodynamics, the kinetic energy, of the quarks and gluons and is the main contributor to the weight of the human body.

Water (H_2O) is the most common molecule inside the cell, contributing to seventy percent of the weight of a cell. In aqueous solutions covalent bonds are much stronger as compared to ionic bonds, hydrogen bonds and van der Waals attractions and much of the biology depends upon the binding of molecules with each other.

Apart from water, almost all other molecules composing a cell are based on Carbon with the most common combinations being methyl ($-CH_3$), amino ($-NH_2$), hydroxyl (-OH), phosphate ($-PO_3$), carboxyl (-COOH) and carbonyl (-C=O). These are essentially the same for all living species and these molecules are composed of a precisely configured set of atoms linked through covalent bonds. Calcium is another very important atom for the cells inside the human body.

Apoptosis and Cancer Cells

Studies have shown that apoptosis starts from a single cell or a cluster of small cells. Inhibition of apoptosis results in initiation and progression of Cancer [1]. Generally speaking, apoptosis may be initiated in two ways [2]:

i) through intracellular signalling transmissions
ii) through the destruction of mitochondria

Most of the existing anti-cancer therapies such as chemotherapy typically stimulate apoptosis in cancer cells.

Nature of Apoptosis

Cytochrome c , a protein, found between inner and outer mitochondrial membrane in a cell, plays a key part in the initiation of apoptosis of a cell. Cytochrome c is attached to the inner membrane due to hydrophobic and/or electrostatic association with Cardiolipin. For apoptosis of a cell:

i) Cytochrome c needs to be released from its association with Cardiolipin
ii) There should be sufficient pores available in the mitochondrial membrane for Cytochrome c to be released to extramitochondrial environment

Once released in the extramitochondrial environment, cytochrome c induces caspase cascade. Activated caspases ultimately leads to apoptosis of a cell.

Cancer cells and apoptosis inhibition

In cancer cells, Bcl-2 protein family plays an important part. The Bcl-2 protein family consists of:

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1) anti-apoptotic – Bcl-2, Bcl-XL, Mcl-1, A1
2) pro-apoptotic Bax, Bak, Diva

The anti-apoptotic proteins can inhibitapoptosis by preventingcytochrome release.Absence of apoptosis leads to sustained cell and hence tumour growth. The mechanism of Bcl-2 inhibiting cytochrome c release into cytosol is as follows:

- Bcl-2 binds to pro-apoptotic proteins such as Bax
- These pro-apoptotic proteins are instrumental in forming pores in the outer membrane of mitochondria.
- Once these pro-apoptotic proteins are bound to Bcl-2, it impacts their ability to form pores.
- Absence of sufficient pores in the outer membrane of mitochondria in turn does not allow the release of cytochrome c to extramitochondrial environment.

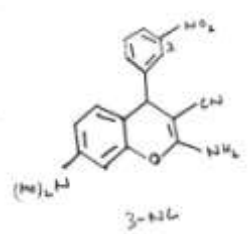
Theoretical Perspective of solving the problem of apoptosis inhibition in cancer cells

There are two theoretical possibilities to overcome this problem:

1. In case of pro-apoptotic proteins being bound by Bcl-2 if an alternate mechanism can be found for forming sufficient pores in the mitochondrial membrane to release cytochrome c into cytosol, it will regulate the apoptotic cell dismantling cycle.
2. To look at ways to promote the number of pro-apoptotic proteins and subdue the number of anti-apoptotic proteins

There is new research [6] that suggests that use of a chromene known as 3NC i.e. 2-amino-4-(3-nitrophenyl)-3-cyano-7-(dimethylamino)-4H-chromene, upregulates Bax and down regulates Bcl2.

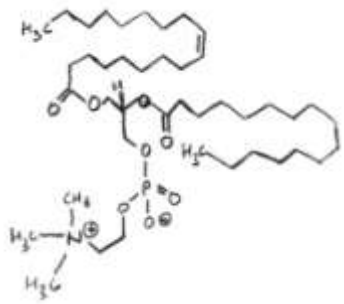
This can potentially help with apoptosis of cancer cells.

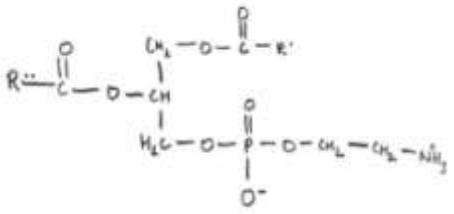


For the proposed second option and the researched potential solution, it is very difficult to regulate the amount of 3NC and deliver it precisely to the tumour cells. Hence, while this is a promising possibility, the implementation of this is very difficult.

So let us look at the first option of increasing the pore formation in the mitochondrial membrane. Let us consider the chemical composition of the mitochondrial membrane.

Phosphatidylcholineand phosphatidylethanolamine constitute almost 40% and 30% of the total mitochondrial phospholipids forming the membranes respectively [7].





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Phosphatidylcholine

Phosphatidylethanolamine

Both phosphatidylcholineand phosphatidylethanolamine have "fatty acid" tails and are the key reason for a lower dielectric constantε (relative dielectric constantof 10) of the mitochondrial membrane as compared to the adjacent cytoplasm that has a relative dielectric constant of 80. [8]

Given the well-known laws of physics for electric field (E): $\varepsilon_1 E_1 = \varepsilon_2 E_2$

The electric field in the membrane will be almost eight times higher than in the adjacent cytoplasm. In case a high electric field is applied to the cell, it will lead to shifting of electrons of the atoms that constitute the cell.

In case the applied electric field is high (range of several hundred kV/cm), it should provide sufficient energy for conformational changes to phosphatidylcholineand phosphatidylethanolamine in the mitochondrial membrane, creating pores in the membrane.

However, there is a risk of the high electric field permanently damaging the membrane leading to its rupture. The ideal mechanism is to apply the electric field for a very short duration, sub nano second duration. Based on the nature and type of tumours being targeted, the number of pulses of such sub nano second duration high electric field pulses can be applied.

If the duration of applied electric field is very small, the electron shifting effect will be temporary and the strong covalent bond forces, along with presence of Ca^+ atoms that can be used to bond can make this change reversable. Effectively ensuring that the behaviour of the cell closely emulates that of a normal cell and provides a pathway for apoptosis through creation of the pores.

II. CONCLUSION

Use of very short duration (sub nano second) high electric field (hundreds of kV/cm range) targeted on cancer tumours should promote reversible pore formation in the mitochondrial membrane, allowing cytochrome c to be released which induces caspase cascade. Activated caspases ultimately lead to apoptotic cell dismantling. The number of pulses to be used depends on the size and location of the tumour inside the human body.

Since the mechanism is reversible and closely emulates the natural healthy cell behaviour, it allows normal modulation of life and death of a cell for maintaining a healthy human body.

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