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Cell Fleeing from Death Phenomenon

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Abstract

Cell fleeing from death phenomenon occurs as either complete or incomplete; the phenomenon is incomplete fleeing from death when cell blocks intrinsic death program only. But, it becomes complete fleeing from death if the cell successfully blocks the pathway of intrinsic and extrinsic programs of cell death. This phenomenon is induced by the formation of hydrogen peroxide which activates nuclear factor kappa B. The nuclear factor-kappa B stimulates the expression of several genes, to produces 6 factors (BcL-2, Muc-1, MMPs, DcR3, Muc-4, muc-16, and TNF-*a*). Such factors act as blockers of the pathway of intrinsic and extrinsic programs of cell death. These blockers convert normal cell to a cancer cell. If these blockers are removed, the death programs of cancer cells will run again and cancer will disappear.

Keywords

Phenomenon, Apoptosis, Cancer

1. Introduction

A phenomenon in science is an extraordinary occurrence or circumstance. There is a big difference between natural phenomenon which we can easily see with our eyes and cellular phenomenon which occur in the cell.

It is so difficult to detect a cellular phenomenon and to track it as it occurs and interpret it. But Allah who created the cell is aware of its phenomena and teaches us about one which has never been known to cell scientists or mentioned before. This phenomenon reveals the right cancer science: description, how does the normal somatic cell transform into a cancerous cell, the real cause of cancer and the right ways to treat cancer.

Quranic verse No. 8 surataljomaa, **"Say to them, the death you try to flee from will meet you; then you will be conveyed back to Him Who knows the Unseen and the Witnessed. Then He will inform you of all that you have**

done."

The death you try to flee from will meet you; this means that when fleeing, the location of the death will be behind you and upon meeting; the death will be in front of you. This means that, the death has two opposite locations and one of them moves toward you and will meet you. This means that the location of death behind you and in front of you at the same moment. Therefore, the verse is talking about trying to flee from one death has two opposite directions or two deaths in opposite directions. But, when we talk about two deaths in opposite directions, it means that we talking about the manner of cell death.

The living cell has two programs of cell death (intrinsic and extrinsic programs of cell death) two deaths in the opposite direction. The death manner, which mentioned in Quranic verse, is identical to the manner of death in the cell.

The death manner of cell is represented by two opposite sides of death (intrinsic death program & extrinsic death program). In addition, the movement of death, as mentioned in the verse, is represented by the immune cells sending ligands to the death cell receptors (extrinsic program of cell death). But the Quranic verse talks about fleeing from death. Thus, this Quranic verse tells us about a cellular phenomenon "Cell fleeing from death phenomenon".

Have you ever heard about the cell fleeing from death phenomenon? (Figure 1).

2. Material and Methods

The normal somatic cell divides through mitotic division into two similar cells. One of them lives and the other dies .it means that the cell has two programs:

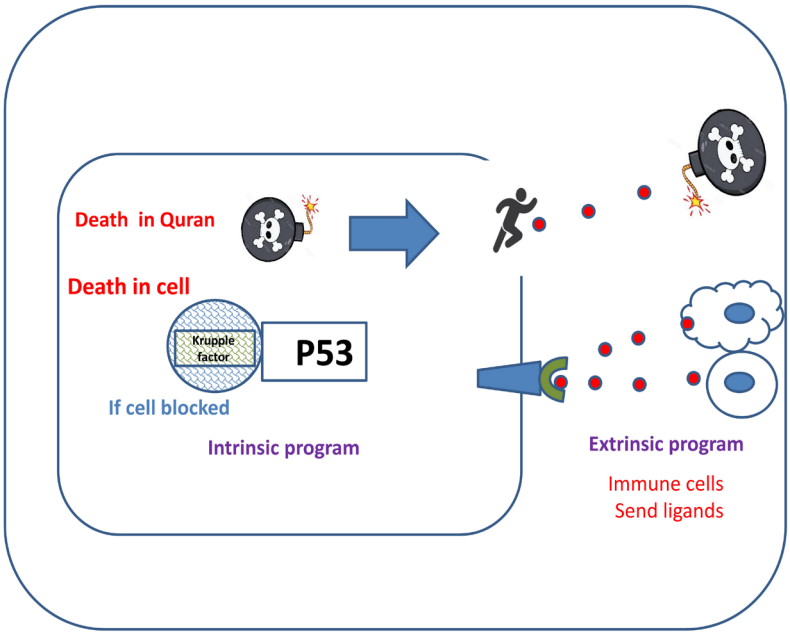

Figure 1. The death in the cell is represented by two opposite locations of death (intrinsic death program & extrinsic death program). In addition, the movement of death, as mentioned in the verse, is represented by the immune cells sending ligands to meet the cell and bind with death receptors.

A division program and a death program and both of them work. Also, cancer cell but both live. It means that the death program my blocked or damage. So, we make a focus on the death program of normal cells and cancer cells. Each living cell has two death programs: an intrinsic program (genetic) and extrinsic program (immune).

The cell death programs help the body get rid of cells it does not need. About 50 - 70 billion cells die each day by apoptosis [1]. Apoptosis produces cell fragments-called (apoptotic bodies) which are quickly removed by phagocytic cells that engulf them before the contents of cell spill out onto the surrounding cells and damage them. Once apoptosis has begun, it cannot be stopped so, it is a highly regulated process [2] [3].

Apoptosis can occur via two different pathways: Intrinsic and Extrinsic.

2.1. Intrinsic Death Program of Cell

The intrinsic pathway is activated as a result of DNA damage [4] and is controlled by the Bcl-2 family of proteins [5]. All the members of the Bcl-2 family share a close homology in up to four characteristic regions termed the (BH-domains). These BH domains are (BH1, BH2, BH3 and BH4). The Bcl-2 family is divided into pro-death proteins (Pro-Apoptosis Proteins) and pro-survival protein (Anti-apoptotic protein) [6].

2.1.1. Pro-Apoptosis Proteins

These promote cell death. Pro-apoptosis proteins are divided according to the number of BH domains into two categories:

1) Pro-apoptotic multi-domains: which contain (BH1, BH2, and BH3) as (Bak and Bax). Bak is an integral membrane protein on the outer mitochondrial surface, whereas Bax is largely cytosolic protein.

2) Pro-apoptotic one-domain: (BH3-only protein) as Noxa, Puma, and Bad. It is a potent mediator of cell death [7] (**Figure 2**).

2.1.2. Anti-Apoptotic Proteins

(Anti-apoptotic protein) suppresses cell death, by controlling the mitochondrial pathway to apoptosis. Such as (Bcl-2, Bcl-Xl, Bcl-W, Mcl-1 and A1). They share BH1, BH2 and in some cases BH3 & BH4 [7].

In the normal state, anti-apoptotic proteins Bcl-2 bind with pro-apoptotic proteins (Bak and Bax). Therefore pro-apoptotic Bak and Bax are present in an inactive form and the kruppel-like factor occupies the promoter region of P53 gene and keeps it in an inactive form.

When DNA is damaged, the kruppel-like factor leaves the promoter region of P53 gene, resulting in the activation of P53 gene which, in turn, activates P21 (cyclin-dependent kinase inhibitor). When p21 is activated it binds with cyclin, resulting in cell division arrest. Also, the activation of P53 gene results in the production of BH3-only protein (Noxa and Puma) resulting in cell death (**Figure 3**).

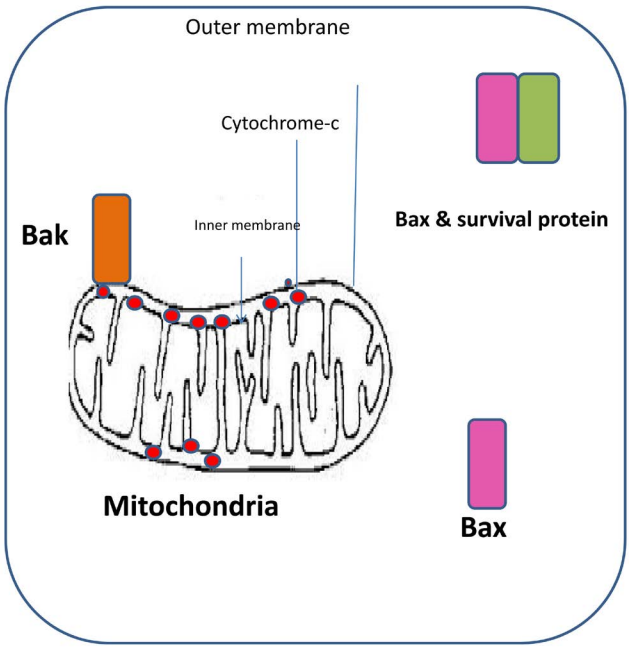

Figure 2. Shows the integral membrane protein (Bak) on the outer mitochondrial surface, whereas Bax is a largely cytosolic protein present in cytosol (free or binding with survival protein).

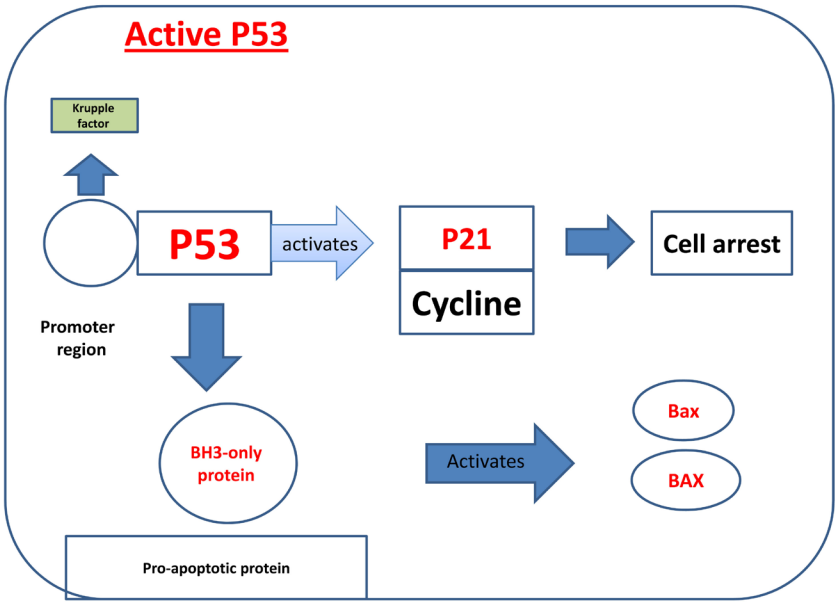

Figure 3. Shows the active state of the cell when DNA is damaged. The kruppel-like factor leaves the promoter region of gene P53 which leads to gene P53 activation and the subsequent activation of P21 (cyclin-dependent kinase inhibitor). P21 then binds with cyclin, resulting in cyclic arrest. The activation of gene P53 also leads to the production of BH-3 only protein, resulting in cell death.

BH3-only protein activates Bax protein; directly and translocates it to the outer mitochondrial membrane or indirectly, by the dissociation of the binding of survival protein with Bax and Bak. This dissociation leads to free Bax–protein in

the cytosol. Then, Bh-3 only protein activates the free Bax and translocates it to the outer mitochondrial membrane [8] [9] [10].

The Bax aggregates on the outer mitochondrial membrane as (Bax-Bax) or (Bax-Bak), forming a channel called the Mitochondrial Apoptosis-Induced Channel (MAC). Once MAC is formed, cytochrome-c is released from the inter-membrane space of the mitochondria to the cytosol [11] [12]. As soon as cytochrome-c is released in the cytosol, it engages the apoptotic protease activating factor-1 (APAF1) and forms the apoptosome, which activates caspase (cysteine aspartic proteases) [13]. Once that happens, apoptosis cannot stop, resulting in cell death [2] [3] (**Figure 4**).

2.2. The Extrinsic Death Program of the Cell (Immune Program)

The activation of the extrinsic program of cell death is executed by tumor necrosis factor receptors, most importantly TNF receptor (TNFR) and Fas receptor (Fas-R). These receptors are activated by specific molecules (Ligands) which are produced by immune cells. These ligands activate their corresponding receptors that are present on the cells, inducing apoptosis [14] [15].

2.2.1. TNF Pathway: TNF Ligand (TRAIL)

TNF-alpha is a cytokine, produced mainly by activated macrophages and monocytes, but can also be produced by many other cells including B-Lymphocytes, T-lymphocytes and fibroblasts. TNF-alpha (cytokine) is the major extrinsic mediator of apoptosis [16] [17]. The interaction between TRAIL and TNFR initiates the pathway that leads to caspase enzyme activation via (FADD) Fas-Associated Death Domain and (TRADD) TNF Receptor Associated Death Domain [18].

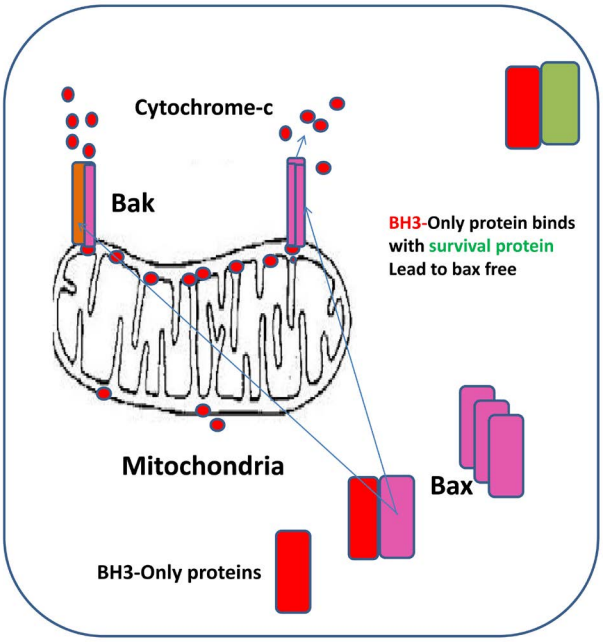

Figure 4. Shows directly and indirectly, activation of Bax protein which presents in the cytosol by BH3-only protein and translocates it to the outer membrane of mitochondria.

2.2.2. Fas Pathway

The Fas receptor is a trans-membrane protein of the TNF family which binds to the Fas ligand (FasL) [19]. In the absence of their ligand, death receptors are present as monomers or pre-assembled dimers or trimmers on the cell surface [20] [21]. Binding of the death-ligand stabilizes the death receptor in trimetric or oligomer complexes and induces a conformational change leading to death receptor activation. The activated receptor complex recruits the adaptor protein FADD and initiates caspases activation (caspase-8 and/or-10), leading to the formation of the death-inducing signaling complex (DISC) [21], which contains the FADD, Caspase-8 and Caspase-10. The caspase-8 directly activates other members of the caspase family (**Figure 5**). In addition, the Fas-disc start a feedback loop that spirals into the increasing release of pro-apoptotic factors from the mitochondria and amplifies activation of caspase [19] [22].

3. Results & Discussion

The cell fleeing from death phenomenon is the ability of the cell to escape death by blocking the intrinsic and extrinsic programs of cell death. The cell refers to this phenomenon to save its life when the cell is severely damaged by excessive free radicals.

The phenomenon is induced by the formation of hydrogen peroxide, either directly as a byproduct of phase-I detoxification enzymes processing or indirectly by converting superoxide free radical (which was generated during the metabolism of harmful substances) to hydrogen peroxide by Superoxide dismutase enzyme (SOD) [23].

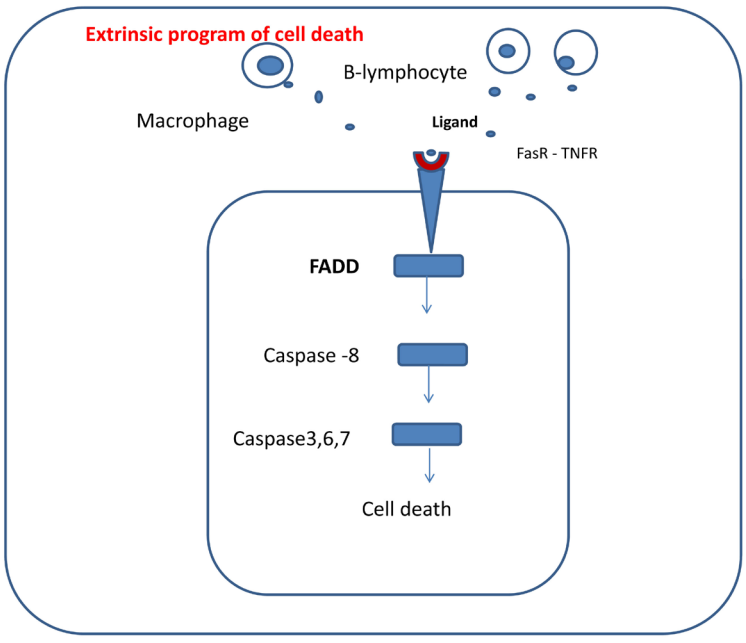

Figure 5. Shows the interaction of ligands with death receptors, which activate the adaptor protein FADD, leading to activate (caspase-8 and/or-10) which activate caspase 3, 6 and 7, leads to apoptosis.

Hydrogen peroxide oxidizes the dynein light chain (LC8), which binds with nuclear factor kappa B (NF-Kb) and its inhibitor kappa B (IKB). This oxidation forms a reversible an intermolecular disulfide bond between the two cysteine (Cys2) residues of LC8 leading to conformational changes, that result in the dissociation of LC8 from IKB [24]. This dissociation allows the kinase enzyme to phosphorylate IKB and leading to its dissociation from nuclear factor-kappa B. Finally, the NF-kB becomes free and translocates into the nucleus and stimulates the expression of several genes (BcL-2, Muc-1, MMPs, DcR3, Muc-4, muc-16, and TNF-α) [25] which are responsible for blocking the intrinsic and extrinsic programs of cell death resulting in this phenomenon (**Figure 6**).

Blocking of cell death programs is as follow:

3.1. Blocking of the Pathway of Intrinsic Programs

Activated NF-kB activates Bcl-2 gene to produce BcL-2 protein (anti-apoptotic protein). This protein is a survival protein which binds with pro-death proteins (Bax in cytosol and Bak at the outer mitochondrial membrane) and keeps them inactive. [26] Also, activates muc-1 gene to produce muc-1 which is a transmembrane glycoprotein that has an extracellular domain and a cytoplasmic domain. The cytoplasmic domain targeted toward the nucleus, where it interacts with the P53 gene and occupies its promoter region. This makes the kruppel-like factor tightly bound with the promoter region, keeping the gene P53 in an inactive form [27] [28], which prevents the production of BH3 only protein (Noxa & puma). Thus, both BcL-2 and muc-1 production leads to shutting down the intrinsic program of cell death (**Figure 7**).

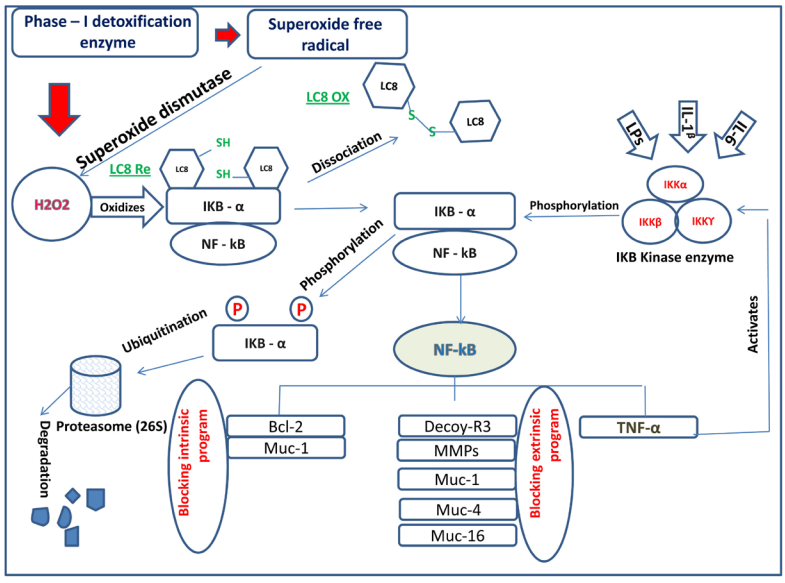

Figure 6. Shows hydrogen peroxide inducing the cell fleeing from death phenomenon By oxidizing the LC8. This oxidation leads in dissociate it from IKB-α, then IKKs phosphorylate the IKB-α resulting in free NF-Kb, which Trans locates into the nucleus and stimulates the expression of genes which responsible for shutdown the pathway of the intrinsic and extrinsic programs of cell death.

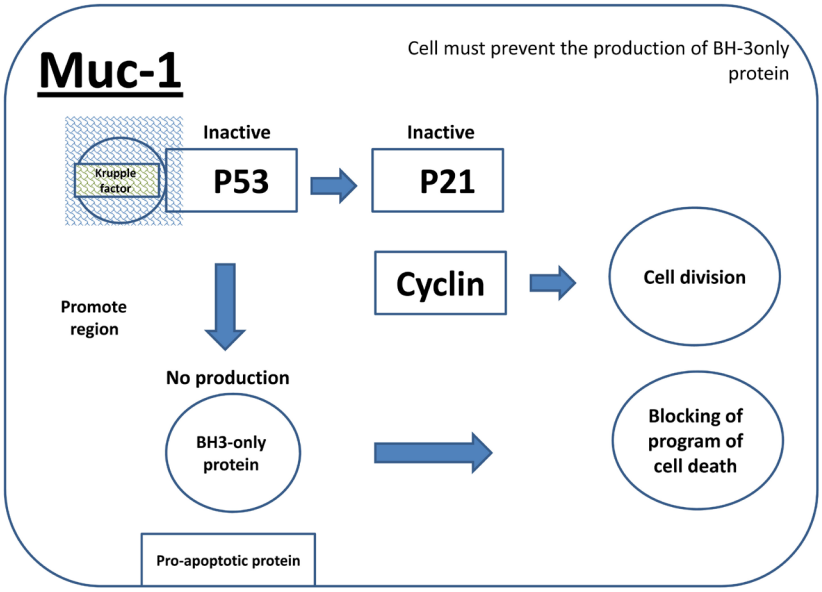

Figure 7. Shows Muc-1 interacting with gene P53 and making the krupple-like-factor tightly bound with the promoter region, leading to the inactivation of the suppression of P21 (cyclin-dependent kinase inhibitor). This results in prevention of cyclic arrest. This also blocks the BH-3 only protein which leads to shut down the intrinsic apoptosis.

3.2. Blocking of the Pathway of Extrinsic Programs

Activated NF-kb up-regulates matrix metalloproteinase enzymes (MMPs), which cleaves the ligands on the surface of immune effector cells, preventing their interaction with the death receptors [29] [30] [31]. In addition, activated NF-kb expresses DcR3 receptors that do not have an intracellular death domain, so they are unable to transmit the death signal into the cell, thus acting as false death receptors. The ligands bind with them instead of binding with true death receptors (FAS). This means that the DcR3 prevents the ligand's interaction with death receptors by competitively binding to death receptors and rendering them inactive [32] [33].

Moreover, activated NF-kb activates TNF-α gene which is responsible for the production of muc-1, muc-4, muc-16 and cytokines [34] [35].

Muc-1 has a cytoplasmic domain and binds directly to the Fas-associated death receptor domain (FADD) and thus inhibiting the extrinsic pathway of the program of cell death [27] [36].

Muc-4 has a long intracellular domain which acts as a protective shield on the death receptors [35] [36].

Muc-16 has a long tower-like extracellular domain which acts as a barrier, preventing access to the death receptors [27] [36].

TNF-α which stimulates the production of cytokine, which activated kinase enzyme which phosphorylates the inhibitor NF-Kb leading to amplify reactivation NF-kB. This means that the cell produces muc-1, muc-4, muc-16, MMPs enzyme, and DcR3 to shut down the extrinsic pathway of the program of cell death (**Figure 8**).

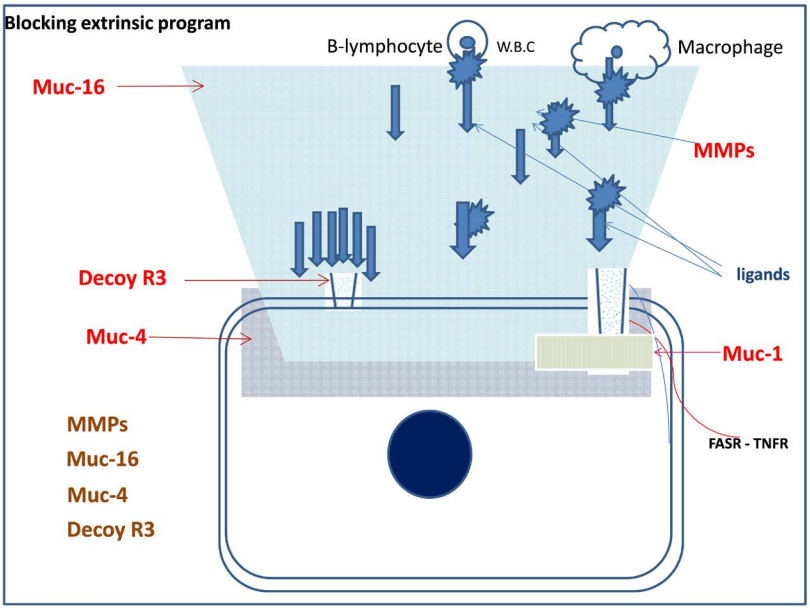

Figure 8. Shows Muc-4 and Muc-16 preventing the binding of ligands with their death receptors and acting like a mask on the death receptors. MMP3 (metalloproteinase enzymes) cleave the ligands at the surface of the immune cells and at the extracellular matrix so that no interactions occur with the death receptor. Decoy receptor-3 binds with ligands and keeps them away from their receptor.

If the cell shuts down only one death program (intrinsic or extrinsic), it means that the fleeing from death is not complete. The cell to completely flee from death has to shut down both programs of cell death. This phenomenon occurs if the cell successfully blocks both intrinsic and extrinsic programs of cell death completely.

Blocking the pathway of the intrinsic program of cell death has two outcomes:

1) The Suppression of p53 gene leads to the suppression of p21 (dependent kinase inhibitor), resulting in the cell's continuous division.

2) The cell prevents the production of pro-death protein BH3-Only protein (Noxa & Puma) and increase the production of bcl-2 (survival proteins), resulting in the continued inactivation of the intrinsic death program. Therefore, by blocking the intrinsic death program, the cell flees from death, but this fleeing is incomplete as the extrinsic program is still active and will send ligands to get the cell to die. However, if the cell succeeds in blocking the extrinsic program of cell death in addition to the intrinsic program, the cell remains alive forever and in a state of permanent division. This makes it a cancer cell. Thus, we can describe cancer as a cellular phenomenon cell fleeing from death by blocking both the intrinsic and extrinsic programs of cell death.

Only one program of cell death is enough to get the cell to die, but Allah created two programs of cell death. Thus, an important question arises in this context: "what will happen if Allah created only one program of cell death" *i.e.* only intrinsic program?

Every day, the human body gets rid of 50 - 70 billion cells that are not needed

by programs of cell death [37]. The work of the intrinsic program of cell death mainly depends on the activity of the p53 gene. When this gene is exposed to physical or chemical injurious agents, the p53 gene may be damaged or genetic mutation is occurred leading to suppress it and loss its functions.

Thus, suppressing its function leads to block the intrinsic program of cell death. If the intrinsic program of cell death is blocked in only one cell among 70 billion cells that die every day, it will result in cancer. Therefore, the probability of cancer occurring in people who have an intrinsic program of cell death only is 50 - 70 billion times daily. Thus, it is impossible for one person or any living creatures to escape from cancer. But, Allah wisely created another program of cell death (an extrinsic program of cell death).

If the cell succeeded to flee from death by blocking the intrinsic program of cell death, the extrinsic program will meet the cell to get it to die by sending ligands to bind with its death receptor (FAS). This is identical to what is mention in Qur'an verse 8, surat aljomaa, "**Say to them, The death you try to flee from will meet you; then you will be conveyed back to Him Who knows the Unseen and the Witnessed. Then He will inform you of all that you have done.**"

In addition, the accuracy of the Quranic pronunciation of fleeing means striving and making the necessary arrangements for saving itself, which is more appropriate than the word escape.

4. Conclusion

The cell is fleeing from death by blocking the pathway of intrinsic and extrinsic programs of cell death. This blocking converts the normal somatic cell to a cancerous cell. Six factors (muc-1, muc-4, muc-16, Bcl-2, MMPs and DcR3) act as blockers of the pathway of intrinsic and extrinsic programs of cancer cell death. If these blockers are removed, the death programs of cancer cells will run again and cancer will disappear.

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Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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