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Quranic Verse No. 8 of Surat Al-Jumu'ah Leads Us to Describe Cancer and Determine its True Cause (Part-II)

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Abstract

Cancer is cell fleeing from death by blocking the intrinsic and extrinsic programs of cell death. The six elements that shut down those programs are: muc-1, muc-4, muc-16, Bcl-2, MMPs and decoy R3. The nuclear factor-kappa B (NF-Kb) stimulates the expression of genes responsible for the production of those elements, which are used by cells to block those two programs. In other words, the nuclear factor kappa B (NF-KB) is responsible for blocking both programs. Therefore, the nuclear factor kappa B (NF-Kb) is the true cause of cancer.

Keywords

Cancer Cause, Muc-1, Muc-4, Muc-16, Metalloprotenase Enzymes (MMPs) Bcl-2, Decoy-R3, NF-KB, Anti-Apoptotic Genes

1. Introduction

Until now, the lives of all cancer patients could not be saved. In order to save the lives of those patients, the true cause of cancer must be determined. All previous studies have not determined the true cause of cancer, but they mentioned the causes related to cancer. The majority of cancers, 90% - 95% of cases, are due to genetic mutations from environmental factors. The remaining 5% - 10% is due to inherited genetics [1]. Some of the leading causes of cancer are: exposure to radiation both ionizing radiation and nonionizing [2] [8], exposure to certain chemical substances called carcinogens [3], excessive body weight [4], certain viruses and bacteria infections [5] [6] [7], hormonal imbalances, which cause

cancers in the genitalia of both males and females [9] and hereditary, but it is rare [10]. After describing cancer, we tried to find its true cause according to our understanding of the Quranic Verse No.8, Surat Al-Jumu'ah.

"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".

This verse is talking about fleeing from death. When you flee, the site of death is behind you and when death meets you, the site of death is in front of you. This means that death has two opposite sites and one of them is moving toward you. This death which is mentioned in the verse is identical to the manner of death of the cell. The death in the cell is represented by two opposite sites 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 cell receptors. That is the core idea of this paper. This is planned as follows:

1) Studying the elements responsible for blocking the intrinsic and extrinsic programs of cell death.

2) Determining the genes responsible for the production of these elements.

3) Studying the factors which stimulate the expression of these genes.

2. Material and Method

Cancer is described as a cell fleeing from death by blocking the Intrinsic and extrinsic programs of cell death (Part-1) [11]. The cell produces six elements to do so. Those six elements (Muc-1, Muc-4, Muc-16, Bcl-2, MMPs and Decoy-R3) have been related to NF-Kb. There is evidence that strongly ensures that the NF-kB has anti -apoptotic function [12] [13].

NF-Kb is a short name for Nuclear Factor Kappa B. NF-Kb is a transcription regulator that is activated by various intra- and extra-cellular stimuli such as cytokines, Interleukin (TNF-a, IL-1 and IL-6), free radicals, ultraviolet irradiation, and bacterial or viral products. [14] [15]. Also, it is strongly induced by H_2O_2 [16].

The NF-Kb transcription factor family consists of five proteins: P65 (RelA), RelB, c-Rel, p105/p50 (NF-Kb1) and p100/52(Nf-Kb2). They associate one another to form active transcription whether homo or heterodimer complexes. They all share the Rel homology domain (RHD). The Rel homology domain mediates the DNA binding, dimerization, interaction with inhibitor-kappa B, as well as nuclear translocation [17] [18]. The NF-kB family of proteins can be further divided into two groups based on their transactivation potential because only p65 (RelA), RelB and c-Rel contain carboxy-terminal transactivation domains (TAD). RelB is unique in that it requires an amino-terminal leucine zipper to its TAD to be fully activating [19]. The Rel protein family members can form up to 15 different dimers. The p65/50 heterodimer clearly represents most of Rel dimers, found in almost all cell types [20]. The active form of NF-kB con-

sists of two different units p50/p56 [21].

In unstimulated cells, NF-Kb proteins are localized in the cytoplasm in an inactive form through their interaction with inhibitor proteins known as IkB. The IKB proteins contain several distinct domains, including ankyrin repeats that is critical for IKB interactions with NF-KB [18].

In order to activate the NF-KB molecules, the cells first need to separate the NF-KB protein from their inhibitors. The IKB protein inhibitor dissociates from Nf-kb dimers and allows the translocation of NF-KB from the cytoplasm into the nucleus.

A variety of stimuli include—Bacterial and viral infections (e.g., through recognition of microbial products by receptors such as the Toll-like receptors), inflammatory cytokines, and antigen receptor engagement which can all lead to the activation of NF-KB. In addition, NF-KB activation can be induced by physical stimuli (UV-Irradiation), physiological stimuli (ischemia and hyperosmotic shock), or oxidative stress [20] [21]. The phosphorylation of IKB proteins is a key step for activation of NF-KB. The phosphorylation of the IKB proteins is mediated by IKB kinases (IKKs). IKKs activity is present in a high-molecular-weight complex containing at least two kinase subunits IKK-α and IKK-β. The IKK-β is the critical kinase in activating the NF-KB pathway, while IKK-α plays an accessory role [22]. The activated IKK complex phosphorylates the IKB protein inhibitor at sites serine 32 and 36, which leading to ubiquitination of it on a lysine (at sites 21 & 22 of IKB). Ubiquitinated IKBs are directed to the proteasome (26S) for complete degradation, enabling the free NF-KB (P65/P50) heterodimers to enter the nucleus [23].

The released NF-KB (P65/50) trans-locates to the nucleus and stimulates the expression of several genes. We are only concerned with the genes that have a role in the shutdown of the intrinsic and extrinsic programs of cell death (**Figure 1**).

2.1. Role of NF-kB in Production of Anti-Apoptotic Protein

The Bcl-2 gene is transcriptionally regulated by nuclear factor-kappa B (NF-kappa B) [24]. Anti-apoptotic genes that are directly activated by NF-KB, include the cellular inhibitors of apoptosis (c-IAP1, c-IAP2, and IXAP), the TNF receptor-associated factors (TRAF1 and TRAF2), the Bcl-2 homologue A1/Bf1-1, and IEX-IL [25] [26]. Bcl-2 plays a critical role in blocking the intrinsic program of cell death by binding with Bax and Bak and keeps them in an inactive form.

2.2. Role of NF-KB in Production of Mucin-1

NF-Kb directly binds to the Muc-1 promoter to activate gene transcription [27]. NF-Kb induces cytokines that regulate the immune response such as (TNF-α, IL1, IL-6 and IL-8) [28] [29]. One of those cytokines, TNF-α stimulates the expression of Muc-1 gene [30].

The Muc-1 is aberrantly over-expressed in human cancer. The Muc-1 is a

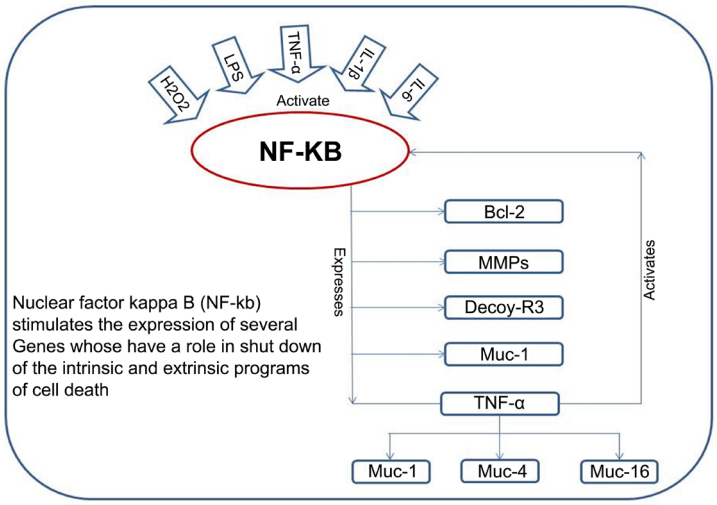

Figure 1. The nuclear factor kappa-B stimulates the expression of several genes whose have a role in shut down of the intrinsic and extrinsic programs of cell death.

trans membrane glycoprotein which has extracellular domain and cytoplasmic domain. The cytoplasmic domain (Muc1-c) is targeted toward the nucleus, where it interacts with p53 gene and occupies its promoter region. This makes the krüppel-like factor tightly bound with the promoter region, resulting in suppression of gene P53 [31] [32]. When gene p53 becomes inactive, this leads to suppression of P21 which results in the prevention of its binding to cyclin. Thus the cell divides endlessly. This also blocks the Bh3-only protein production (Noxa and Puma) which leads to blocking of the intrinsic program of cell death which result in keeping cell alive. Furthermore, the cytoplasmic domain of Muc-1 is associated with Bax in human cancer cells and binds directly to Bax forming Bax-BH3 complex, thereby blocking Bax function, which results in repressing the mitochondrial pathway of cell death [33].

2.3. Role of NF-KB In Production of MUC4

As mentioned above, NF-Kb induces cytokines that regulate the immune response such as (TNF-α, IL1, IL-6 and IL-8) [28] [29]. Likewise, TNF-α stimulates the expression of Muc-4 gene [30].

Mucin-4 consists of a large extracellular alpha subunit that is heavily glycosylated and a beta subunit that is anchored in the cell membrane and extends into the cytosol [34]. The beta subunit is considered an oncogene. This subunit serves as a ligand that causes the phosphorylation of ErbB2 which is suggested to cause the repression of the extrinsic pathway of the program of cell death [35] [36].

2.4. Role of NF-KB in Production of Muc-16

NF-Kb induces cytokines that regulate the immune response such as (TNF-α, IL1, IL-6 and IL-8) [29] [30]. Likewise, TNF-α, stimulates the expression of Muc-16 gene [31] which stimulates the production of mucin-16 which has long extracellular domain (tower-like) that acts like a mask on death receptors, re-

sulting in prevention of ligands binding with the death receptors and contributes to the blocking of extrinsic program of cell death [37] [38].

2.5. Role of NF-KB in Activation of MMPs

The activation of the NF-kB pathway induces downstream target genes, including MMPs [39]. NF-kb up regulates matrix metalloproteinase enzymes (MMPs) [40]. These enzymes are capable of degrading all kinds of extracellular proteins [41]. Matrix metalloproteinase is an anti-apoptotic factor as it cleaves the ligands preventing their interaction with the death receptors.

2.6. Role of NF-kB in Activation of Binding of Decoy-R3 and Ligands

Decoy receptor-3 gene, also known M68; TR6, DcR3, is located in a gene-rich cluster on chromosome 20. This gene belongs to the tumor necrosis factor receptor superfamily. It acts as a decoy receptor that competes with death receptors for ligand binding. DcR3 is highly elevated in patients with various tumors [42]. Recent studies have shown that the expression of DcR3 is stimulated by TNF-α. In addition, it has been determined that NF-kB activation is essential for DcR3 expression [43]. The expression of c-Rel or activation of endogenous Rel/NF-Kb factors has been reported to up-regulate TRAIL-DcR3 interaction. The interaction between ligands and Decoy receptor-3 (TRAIL-R3) is a potential anti-apoptotic member. NF-Kb reinforces the binding between the ligands and decoy R3. Therefore, the ligands cannot bind with their specific death receptor (FasR/NFTR) preventing the pathway of the extrinsic program of cell death [44].

3. Discussions

Cancer is described as a cell fleeing from death by blocking the intrinsic and extrinsic programs of cell death. The cell produces six elements that block the intrinsic and extrinsic programs of cell death. Those elements are Muc-1, Muc-4, Muc-16, survival proteins (BcL-2), Decoy-R3 and Matrix Metalloproteinase enzymes. By following the sources of production of those elements, we discover NF-Kb. When NF-Kb becomes active, it translocates into the nucleus and stimulates the expression of several genes. Those genes have a critical role with the intrinsic and extrinsic programs of cell death.

NF-kB stimulates the expression of Muc-1 gene directly or indirectly by inducing cytokines (TNF-α) which stimulate the expression of Muc-1 gene to produce mucin-1. Muc-1 is aberrantly over-expressed in human cancer. The cytoplasmic domain (Muc-1-c) is targeted toward the nucleus where it interacts with the p53 gene and occupies its promoter region. This makes the krüppel-like factor tightly bound with the promoter region resulting in suppression of gene P53. When genes p53 becomes inactive, this leads to the suppression of P21 which results to the prevention of its binding to cyclin. Thus the cell divides endlessly. This also blocks the BcL-3 only protein production as (Noxa & Puma).

Furthermore, the cytoplasmic domain of Muc-1 binds directly to Bax and Bak in human cancer cells and blocks its function, thus leading to blocking the intrinsic program of cell death.

NF-Kb stimulates the expression of BcL-2 (survival protein) production, also leading to blocking the intrinsic program of cell death.

So, nuclear factor kappa B (NF-Kb) is responsible for blocking the intrinsic program of cell death.

It induces cytokines that regulate the immune response such as (TNF-*α*, IL1, IL-6 and IL-8). One of those cytokines, TNF-*α*, stimulates the expression of Muc-1gene, Muc-4gene and Muc-16 gene. Muc-1 gene stimulates the cytoplasmic domain of mucin-1 and binds directly to Fas-associated death domain (FADD) at the death effector domains, so Muc-1 competes with caspase-8 for binding to FADD. It inhibits the extrinsic program of cell death.

NF-Kb stimulates the expression of TNF-*α* gene which stimulates the expression of Muc-4 gene. Muc-4 gene stimulates the production of mucin-4 which has a beta sub unit that is anchored in cell membrane and extends into cytosol. This subunit serves as a ligand that causes the phosphorylation of ErbB2 which is suggested to cause the repression of the extrinsic pathway of the program of cell death.

NF-Kb stimulates the expression of TNF-*α* gene which stimulates the expression of Muc-16 gene. Muc-16 gene stimulates the production of mucin-16 which has long extracellular domain (tower-like) which acts like a mask on death receptors, resulting to the prevention of ligands binding with the death receptors and contributing to the blocking of the extrinsic program of cell death.

Recent studies have shown that the expression of DcR3 is stimulated by TNF-*α*. TNF-*α* is stimulated by NF-kb. So, NF-KB is responsible for the activation of decoy-R3 which is highly elevated in patients with various tumors. It does not have intracellular death domain, so it is unable to induce apoptosis. It binds to FasL, LIGHT, and TL1A. The crystal structure of FasL was shown in complex with DcR3. So, it keeps the ligands away from the death receptors leading to blocking the extrinsic program of cell death.

NF-kb up regulates matrix metalloproteinase enzymes (MMPs). These enzymes are capable of degrading all kinds of extracellular proteins. Matrix metalloproteinase is an anti-apoptotic element as it cleaves the ligands preventing their interaction with death receptor. So, matrix Metalloproteinase enzyme blocks the extrinsic program of death by cleaving the ligands.

So, nuclear factor kappa B (NF-Kb) blocks the extrinsic program of cell death.

We deduce from the above that, the nuclear factor kappa B (NF-Kb) is responsible for blocking both the intrinsic and the extrinsic programs of cell death. Therefore, the nuclear factor kappa B (NF-KB) is the true cause of cancer.

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