Insight Cross-talk between p53 and Toll-like Receptor

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Authors’ contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Toll-like receptors (TLR) are one of the most-studied receptors for their role in innate immunity. TLRs are reported to binds with conserved pathogen-associated molecular patterns (PAMPS). TLRs and PAMPS interaction leads to several downstream proteins’ activation, which further signaled to the various transcription factors. Moreover, these transcription factors play an important role in synthesizing proteins that control cellular immunity. Various TLR proteins have been reported in humans as well several other organisms. Studies show that apart from inducing innate immunity, TLRs have also played an important role in the induction of many proteins, and protein networks associated with initiation apoptosis and cancer prevention. P53 is one of the most important and widely studied proteins. Moreover, various experimental studies suggest that p53 has an important role as tumor suppressor. It is reported that more than 50% of cancerous growth are associated with the mutation of p53. It acts as transcription activator for several proteins that are mostly associated with glycolysis, cell cycle, cell differentiation, apoptosis and cancer. In the*

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present review, we present an insight cross-talk between p53 and Toll-like receptor. In addition, the well-characterized role of p53 in the regulation of the immune system is studied, which would provide a new insight to the broad understanding of p53 role in human biology. Moreover, the association of the p53 and TLRs can lead to therapeutic interventions.

Keywords: Toll-like receptor; p53; pathways; interaction; Apoptosis; Cancer.

1. INTRODUCTION

The innate immunity system is considered as the first liner of defense systems against invading bacterial, viral and fungal infections. Various cells and cellular components play an important role in innate immunity, such as macrophages, dendritic cells, mast cells, neutrophils, and epithelial cells. The coordinated behaviors of each of the cells are responsible for innate immunity [1]. These cells have specialized receptor proteins, which are very much responsible for recognizing and activating other immunity systems such as adaptive immunity. One of the most important receptors proteins are PRRs (pattern recognition receptors). PRRs are specialized in functions as they recognize repeating patterns of pathogen’s molecular structures, known as PAMP (pathogen-associated molecular pattern). PAMP are unique structures which present only on microbial surfaces but are absent in humans. PRRs are expressed in the plasma membrane of innate immunity cells as well as on various cellular components such as endosomes, lysosomes and in the cytosol [2-5]. PRR are able to detect extracellular as well as intracellular pathogens. There are various types of PRRs have been reported. PRR can recognize multiple types of pathogenic species that share a particular type of molecular patterns. TLRs are reported as the first sub-family of pattern recognition receptors (PRRs). TLRs were first discovered in 1985 by German scientists Christiane Nusslein-Volhard Drosophila fruit fly embryo as Toll gene. Toll has been studied for their role in flies development and protection against infection. TLRs are membrane-spanning proteins, i.e., it always attached with a membrane.

P53 protein is mostly studied for their role in apoptosis and in various types of cancers. It has a wide cellular network and plays as an important precursor of various metabolic processes such as, apoptosis, cell-cycle arrest, senescence, glycolysis, TCA cycle, differentiation, cell fate. P53 is known as tumor suppressor gene. It helps in tumor clearance to prevent cancer cell formation. P53 protein activation is reportedly due to response to a variety of cellular stress, such as, hypoxia, nucleotide depletion, nitric oxide, DNA damage. Recently, It is reported that it can also be activated by various signaling molecules such TLRs. In many cancer cells progression, p53 protein is usually found in the inactivated condition. p53 act as a transcription factor of various cellular proteins such as MDM2, p21, Fas, Bax, p48, PTEN, B99, PAI [6-9].

Recently, various experimental studies reported that apart from role in innate immunity, TLRs also participate in signaling of various protein and protein network which are directly and indirectly related to apoptosis and suppression of cancer progression [10]. Moreover, the interaction of TLRs with p53 and its signaling network has also been reported [11-12].

In this present review, we are providing an overview of cross-talk between p53 and Toll-like receptors. We reviewed molecular interaction mechanisms of TLRs in innate immunity, the role of TLRs in activation of p53, the role of p53 in TLRs activation. Moreover, as the p53 protein is a prime focus of this review, the role of the p53 will be well explained in the immune system regulation. The study will provide a new insight to the wider role of p53 in human biology. Further, molecular interaction mechanisms between the p53 and TLRs can lead to therapeutic interventions and possibilities.

2. TLRs IN CELLULAR IMMUNITY: MOLECULAR INTERACTION

The role of TLRs in cellular immunity has been widely reported by several experimental as well as theoretical research articles. They are membrane-bound proteins. Structurally it has two domains i.e. extracellular domains, which are rich in leucine protein and TIR (Toll-like Interleukin Receptor) domain [13]. So far, there are more than 20 TLRs have been identified so far in various animals (Table 1). In human there are 10 functionally known TLRs has been reported. Each of the TLRs in human is identifying a particular type of pathogen-associated molecular pattern. It is also reported that some of the TLRs
(TLR3, TLR 4, TLR 5, TLR 7) interact alone, whereas some TLRs (TLR 1, TLR 2 and TLR 6) interact as a dimer with pathogen-associated molecular pattern (Table 2). Moreover, among the reported TLRs, TLR 10 is found to be exception of all TLRs as which is anti-inflammatory. It inhibits TLR 2 signaling mechanisms. It promotes the expression of IL-1RN (Interleukin 1 receptor antagonist). IL-1RN is well known as anti-inflammatory protein [10], [11], [12-19].

The molecular mechanisms of action of almost all LTRs are reported to be same. As the foreign pathogens such as bacteria, virus and fungus, enters into to bloodstream, are recognized by various types of innate immune system's cell families such as macrophages, dendritic cells, mast cells, neutrophils, epithelial cells by various TLRs which act as first line of defense. TLRs interact at their leucine rich extracellular domains with pathogen-associated molecular structures or patterns such as lipopolysaccharide.

### Table 1. TLR and organism

| TLR   | Organism                                                                 |
|-------|--------------------------------------------------------------------------|
| TLR 1 | Mouse, Human, Chicken,                                                  |
| TLR 2 | Mouse, Human, chicken, Bovine, Dog, Zebu, Chimpanzee, Gorilla, Hamster, |
|       | Rhesus macaque, Guinea Pig, Horse Goat, Sheep, Giraffe, Rabbit, Panda,  |
|       | Newt, Sperm Whale, Deer, Bank Vole                                      |
| TLR 3 | Mouse, Human, Rat, Chicken, Pig, Chameleon, Opossum, Cat, Gorilla,     |
|       | Panda, Baboon, Monkey, Horse, Goat, Elephant, Bovine, Guinea Pig, Bat,  |
|       | Dog, Rhesus macaque, Whale, Red Fox, Wild Turkey, Platypus, Tortoise,   |
|       | Zebra fish, Newt, Dolphin                                                |
| TLR 4 | Mouse, Human, Rat, Chicken, Pig, Cat, Gorilla, Chimpanzee, Orangutan,  |
|       | Bovine, Elephant, Bat, Red Fox, Monkey, Rhesus macaque, Whale, Red Fox,  |
|       | Wild Turkey, Guinea Pig, Sheep, Hamster, Opossum, Panda, Rabbit         |
| TLR 5 | Mouse, Human, Rat, Zebrasfish, Deer, Bovine                              |
| TLR 6 | Mouse, Human, Rat, Zebrasfish, Deer, Bovine, Horse, Pig, Opossum, Dog,  |
|       | Rhesus macaque, Galago, Green monkey, Sheep, Orangutan, Goat, Guinea    |
|       | Pig, Wild Turkey, Rabbit, Squirrel, Turtle, Cat, African Elephant,      |
|       | Giant Panda, Bat, Polar Bear, Red Fox,                                  |
| TLR 7 | Mouse, Human, Rat, Zebrasfish, Deer, Bovine, Rhesus macaque, Chicken,   |
|       | Cat, Chameleon, Chimpanzee, Sheep, Guinea Pig, African Elephant, Dog,    |
|       | Wild Turkey, Polar Bear, Newt, Giant Panda, Beluga Whale, Monkey, Goat  |
| TLR 8 | Mouse, Human, Rat, Zebrasfish, Deer, Bovine, Horse, Opossum, Squirrel,  |
|       | Pig, African Elephant, Chimpanzee, Bat, Polar Beer, Orangutan, Polar    |
|       | Beer, Gorilla, Hamster, Sheep, Green Monkey, Beluga Whale               |
| TLR 9 | Mouse, Human, Rat, Zebrasfish, Deer, Bovine, Dog, Pig, Cat, Horse,     |
|       | Sheep, Zebu, Bat, Beluga Whale, Wild Yak, Rabbit, Red fox, Goat, Donkey, |
|       | Opossum, Gorilla, Chimpanzee, Koala, Orangutan                          |
| TLR 10| Mouse, Human, Rat, Zebrasfish, Bovine,                                  |
| TLR 11| Mouse, Rat                                                               |
| TLR 12| Mouse                                                                    |
| TLR 13| Mouse                                                                    |

### Table 2. TLR and ligands

| TLR  | Location     | Ligands                                             |
|------|--------------|-----------------------------------------------------|
| TLR 1| Cell Surface | Bacterial lipoglycans, Bacterial lipopeptide        |
| TLR 2| Cell Surface | Bacterial lipoglycans, Bacterial Peptidoglycans      |
| TLR 3| Endosomal    | Double Standard viral RNA                           |
| TLR 4| Cell Surface | Bacterial Lipopolysacharrides                       |
| TLR 5| Cell Surface | Bacterial Flagellin                                 |
| TLR 6| Cell Surface | Bacterial lipoglycans, Bacterial Peptidoglycans      |
| TLR 7| Endosomal    | Single stranded viral RNA                           |
| TLR 8| Endosomal    | Single stranded viral RNA                           |
| TLR 9| Endosomal    | Bacterial unmethylated CpGoligo nucleotides         |
| TLR 10| Cell Surface | Bacterial lipoglycans, Bacterial Peptidoglycans     |
Fig. 1. A schematic diagram of molecular interaction of toll like receptor glycoprotein, bacterial flagelin, single-stranded RNA, and double-strand RNA. This interaction leads to the activation of the TIR domain, an inter-membrane domain [20-25]. Further, the activated TIR domain initiates the recruitment of several adaptor proteins such as MYD88, TRAM, TIRAP, TRIF, TRAF, etc. The interaction of these adaptor proteins with TIR domains leads to a signaling cascade. Further, MYD88 interacts with IRAK (IL-1R associated kinases) and TRAF (TNF-receptor-associated factor) proteins. These proteins upon activation, interact with transcription factor IRF (Interferon regulatory factor).

Further, IRF enters into the nucleus to attach promoter regions of various cytokines and chemokine’s such as ILs (interleukins), IFNs (interferon), CD(cluster of differentiation) proteins. Moreover, ILs are pro-inflammatory proteins, which activates white blood cells to recruit neutrophils and other scavengers of the pathogen. IFNs acts against viral factors. CDs proteins interact and stimulate acquired
immunity cells such as TCell, B-Cell, and NFK Cells.

3. TLRS AS REGULATOR OF P53 SIGNALING: MOLECULAR MECHANISM

Various studies suggested that in gastric cancer cells, TL4 is correlated with various tumor stages. It is reported that TL4 elevate the production level of reactive oxygen species (ROS). Upon binding of PAMP on LRR (leucin rich receptor) extra-membrane domain of TLR, the intra-membrane domain of almost all TLRs get activated which further recruit MYD88 protein. This leads to IRK1 and IRK4 activation. Further, these activated proteins transmit signal to TRAF6 protein. TRAF6 protein stimulates IKK proteins [9], [11], [12], [30-35]. The activated form of IKK proteins phosphorylates kB which leads to an activated form of NF-kB. There are some MYD88 independent pathway has also been reported to stimulate NF-kB which is found in TLR 3 signaling via TRIF protein. After activation NF-kB enters into the nucleus, enhancing the transcription in various proteins such as A20, IEX-1L, TRAF1, TRAF2, IAP1, and IAP2. These transcribed proteins have an important role in the inhibition of apoptosis. Moreover, various experimental studies reported that NF-kB protein suppresses the transactivation activity of p53 protein [36].

4. P53 AS REGULATOR OF TLRS: MOLECULAR MECHANISM [26-29]

P53 is a well-known transcription factor. It promotes the transcription of many proteins associated with cell cycle, cell growth, cellular differentiation, cellular apoptosis, and cellular inflammation. Almost all TLRs are found to be interacted with p53 either canonically or non-canonically. Recent studies suggested that TLRs have a p53 responsive element sequence by which p53 targets TLR to regulate their expression [37].

Moreover, various studies suggested that the expression levels of TLRs 2, 3, 4, 5, 6, 7, and 9 increases due to DNA damage in accordance with p53 induction [11], [12], [37]. Various reports suggested that TLR 2, TLR 3, TLR 5, TLR 6 can enhance the cellular apoptotic pathways. The enhancement of apoptotic pathway by these TLRs takes place either in correlation with p53 protein or as independent of p53 protein [38]. Various studies reported that the dimer of TLR1/TLR2 and TLR2/TLR6 after activation via PAMP activates the PI3K-AKT pathway. The activation of PI3K-AKT pathway by these TLRs dimers initiate through its recruitment of Rac1 protein at its TIR domain. The activated forms of Rac1 further interact with PI3K protein, which leads to the phosphorylation of PI3K proteins. Activated form of PI3K protein interacts with AKT protein. Moreover, the AKT protein further activates NF-kB protein, which leads to the transcription of the inflammatory protein. However, on the other hand, AKT protein also activates as well as suppresses various proteins, which are directly involved in apoptosis. It activates MDM2 protein, which is found to be negative regulator of p53 protein, leads to its degradation. This degradation of p53 protein increases cell survival and decrease in cellular apoptosis. Recently, it was reported that an activated form of p53 enhances TLR 3 mRNA production in various cancer cell lines such lung, hepatic-carcinoma, breast, gastric, epithelial cells [39]. Upon activation by ds viral RNA, TLR3 recruits TRIF adaptor protein via its TIR domain. This induced TRIF protein further interacts with RIP1 protein. Additionally, the activated RIP1 transfer signal to caspase-8 protein. Caspase-8 leads to the activation of apoptotic cascade protein leading to cellular apoptosis [40].

5. CONCLUSION

TLR gene family directly as well as indirectly interacts with p53 protein via without stress or with stress caused by virus, and fungal infections. The role of p53 in regulation of the immune system is studied, providing a new insight into the broad understanding of p53 role in human biology. Moreover, P53 and TLR interaction in cancer and other disease leads to therapeutic studies in cancer treatment.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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