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Toll like Receptors and High Mobility Group Proteins relation with MicroRNAs in Melanoma

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Abstract: Back ground:Recently miRNAs found as an important cancer therapy targets in innate immunity. Therefore these molecules have important role in the processing of many biological responses, such as cell proliferation, apoptosis, and stress responsiveness. MiRNAs expression significantly change on tumor cells; some miRNAs that negatively regulates oncoproteins. These miRNAs are known as tumor suppressor miRNA and oncogenic miRNA. MiRNAs have major relation with damage and pathogen associated molecular patterns by innate immunity signaling pathways such as toll like receptors. Toll like receptors discovered in drosophila. Toll like receptors can induce cytokines in inflammation and cancer. High Mobility Groups are danger proteins which can involve in damage associated molecular pattern and manage with Micro RNAs. The aim of this review is finding the relation of Melanoma miRNAs with innate immune system signaling such as toll like receptors and the proteins such as high mobility group box 1.
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Running title: Toll like Receptors and MicroRNAs in Melanoma

Abbreviation:

pattern recognition receptors (PRRs)
pathogen associated molecular patterns (PAMPs)
Toll like receptors (TLRs)
micro RNA (miRNA)
High Mobility Groups (HMG)
lipopolysaccharide (LPS)
heat shock proteins (HSPs)
Tumor Necrosis Factor(TNF-α)
competing endogenous RNA (ceRNA)
Signal transducer and activator of transcription(STAT)
Necrosis Factor (NF-kB)
Interleukin-1 receptor-associated kinase(IRAK)
TNF receptor associated factors(TRAF)
Interferon regulatory factor(IRF)
Myeloid differentiation primary response gene 88 (MYD88)

Introduction:

The innate immune system, also known as the nonspecific immune system is an evolutionarily older defense strategy that comprises the cells and mechanisms that defend the host from infection by other organisms(1). It relies on "pattern recognition" which can recognize by pattern recognition receptors (PRRs) and they recognize pathogen associated molecular patterns (PAMPs)(2). Toll like receptors (TLRs) are a type of PRR and recognize molecules that are broadly shared by pathogens but distinguishable from host molecules, collectively referred to as PAMPs(3). TLRs bind and become activated by different ligands, which, in turn, are located on different types of organisms or structures(4). They also have different adapters to respond to activation and are located sometimes at the cell surface and sometimes to internal cell compartments(5). Furthermore, they are expressed by different types of leucocytes or other cell types. A micro RNA (miRNA) is a small non-coding RNA molecule (containing about 22 nucleotides) found in plants, animals and some viruses, that functions in RNA silencing and post-transcriptional regulation of gene expression(6). Recently studies discovered the relation with miRNA and immunity in cancer(7, 8). The first human disease known to be associated with miRNA deregulation was chronic lymphocytic leukemia(9). Many other miRNAs also have links with cancer and accordingly are sometimes referred to as "oncomirs"(10). One type of these cancers is a melanoma. Melanoma is the most dangerous type of skin cancer that develops from the pigment-containing cells known as melanocytes(11). Melanomas typically occur in the skin but may rarely occur in the mouth, intestines, or eye. In women they most commonly occur on the legs, while in men they are most common on the back(12).

MicroRNAs in Melanoma

miRNAs expression significantly change on tumor cells; some miRNAs regulates oncoproteins which can down regulate during malignant transformation cells while others that target mRNA of tumor suppressors are up regulated(13). Table 1 summarizes the main functions of miRNAs which involve in melanoma (10, 13-15).

HMG groups and functions:

HMG proteins are ubiquitous nuclear proteins that regulate and facilitate various DNA-related activities such as transcription, replication, recombination and repair(16). HMGs bind to DNA and chromatin and act as "architectural elements" that induce both short- and long-range changes in the structure of their binding sites(17). They affect the activities of various regulatory molecules, including hormone receptors, p53 and the RAG proteins(18). HMG proteins are thought to play a significant role in various human disorders. Disruptions and rearrangements in the genes coding for some of the HMG proteins are associated with some common benign tumors(19). Antibodies to HMG proteins are found in patients suffering from autoimmune diseases and cancers(20).

TLRs Ligands and signaling

TLRs are believed to function as dimers. Though most TLRs appear to function as homodimers, TLR2 forms heterodimers with TLR1 or TLR6, each dimer having different ligand specificity(21). TLRs may also depend on other co-receptors for full ligand sensitivity, such as in the case of TLR4's recognition of lipopolysaccharide (LPS)(22). Activation of these receptor leads to production of inflammatory cytokines as well as type I interferon's (interferon type I) to help fighting viral infection(23). The adapter proteins and kinases that mediate TLR signaling have also been targeted. When activated, TLRs recruit adapter molecules within the cytoplasm of cells in order to propagate a signal(24). Four adapter molecules are known to be involved in signaling. These proteins are known as MyD88, Tirap (also called Mal), Trif, and Tram (toll-like receptor 4 adaptor protein)(21). TLRs have been suspected of binding to host molecules including fibrinogen (involved in blood clotting), heat shock proteins (HSPs), HMGB1, extracellular matrix components and self DNA (it is normally degraded by nucleases, but under inflammatory and autoimmune conditions it can form a complex with endogenous proteins, become resistant to these nucleases and gain access to endosomal TLRs as TLR7 or TLR9(25). These endogenous ligands are usually produced as a result of non-physiological cell death. Figure 1 summarizes the TLRs ligands and signaling.

MicroRNAs and TLRS

Several miRNAs involved as up regulated mechanisms in response to TLR ligands, and many of them directly target components of the TLR signaling pathway(26). TLR signaling must be strictly regulated immunity and reply to pathogens. Recently miRNAs as a newly discovered class of gene regulators which bind to the 3′region of target mRNA. Some of miRNAs, such as miR-155, miR-Let7 a/b and miR-146a, has confirmed to be key TLR signaling modulators and, importantly, these miRNas are organized by endotoxin-responsive genes(27).

Let7 relation with TLRS and HMG proteins

Let-7 miRNA family members are widely considered to be melanoma suppressors. There are 13 different let-

7 family members in humans such as let-7a-1, let-7a-2, let-7a-3, let-7b, let-7c, let-7d,
let-7e, let-7f-1, let-7f-2, let-7g, let-7i, miR-98, and miR-202(15). let-7 activates Toll-like receptor 7 and causes degeneration in cancer tissues(28). MiR let-7 is a main regulator of gene expression in the central nervous system and cancer which can expressed in macrophages(29). Let7 can directly bind to TLR-7 in mice and TLR-8 in human macrophages and induce the secretion of pro-inflammatory cytokines such as TNF-α and IL-6(30).
Consequently, miRNAs can function as agonists of the TLR7 which is important to NF-κB signaling activation and secretion of pro-inflammatory cytokines(24). Recent studies showed that the Let-7b Is Involved in the inflammation and immune responses associated with helicobacter pylori infection by targeting toll-like receptor 4(31). Let-7e declines the expression of TLR4 on the surface of macrophages and let-7i has antagonist relation with TLR4 protein in human cholangiocyte after Cryptosporidium parvum (C.parvum) infection. Let-7 has also been implicated in the negative regulation of TLR4, the major immune receptor of microbial lipopolysaccharide and down-regulation of let-7 both upon microbial and protozoan infection might elevate TLR4 signalling and expression(31). Let-7 has been demonstrated to be a direct regulator of RAS expression in human cells. All the three RAS genes in human, K-, N-, and H-, have the predicted let-7 binding sequences in their 3'UTRs(32). HMG have three superfamilies' which are (HMGA, HMGB, and HMGN). HMGA proteins characterize by an AT-hook(33). They code for a "small, nonhistone, chromatin-associated protein that has no intrinsic transcriptional activity but can modulate transcription by altering the chromatin architecture. HMGA1 can initiative tumor progression to a stem cell-like state(33). HMGA1 was defined to bind the STAT3 can upregulate its expression in Melanoma cell line. The HMGA1 and HMGA2 genes were expressed in several cancer types but inattentive in adult healthy tissues. HMGA2 as protein and as a competing endogenous RNA (ceRNA) was described to modify gene expression by activation of Let7(34). HMGA1, HMGA2 are regulators of let-7 in melanoma. Which their negatively regulated by let7.Let-7 directly inhibits HMGA2 by binding to its 3'UTR(35). Removal of let-7 binding site by 3'UTR deletion causes overexpression of HMGA2 and formation of tumor(35). Then let-7a expression indirectly blocks STAT3 transcription(35). STAT3 activation is necessary to NF-kB activation. HMGB1 is another superfamily of HMG proteins which stimulate DNA binding of several steroid receptors including the let-7. HMGB1 was not a direct let-7 target, its expression is modulated by HMGA1(35). Recent studies showed that The tumor suppressor p53 can downregulate the activity of the HMGB1 promoter and decrease of let-7a and let-7b expression in human melanoma(35, 36).

MiR-155 relation with TLRs and HMG groups

MiR-155 is a microRNA that in humans is encoded by the MIR155 host gene or MiR155HG(37). MiR-155 plays a role in various physiological and pathological processes. The miR 155 negatively regulates TLR signaling by targeting MyD88(37). miR-155 is involved in immunity by playing key roles in modulating humoral and innate cell-mediated immune responses(29). In miR-155 deficient mice, immunological-memory is impaired; making it fall prey to repetitive bouts of invasions by the same pathogen, maturation and specificity of miR-155-deficient B-lymphocytes are impaired since the process relies on AID enzyme which has a miR-155 target in its 3' UTR end. Activated B and T cells show increased miR-155 expression, the same goes for macrophages and dendritic cells of the immune system(38). MiR-155 is crucial for proper lymphocyte development and maturation. In macrophages, miR-155 is up regulated in reaction to the TLR3 ligand and CpG (TLR-9)(38). MiR-155 appearance is also induced by TLR signaling. Upon its beginning via activation of TLRs by pathogen stimuli miR-155 functions as a regulator of innate immune signaling pathways(39). MiR-155 is up regulated by HMGB1 in derived damage associated molecular pattern molecules. Also HMGB1 induced inflammatory effect which is blocked by MiR155 in melanoma(40).

MiR-146 relation with TLRs and HMG groups

The miR-146a gene is located on human chromosome 5, while miR-146b is located on chromosome 10(41). The mature sequences for miR-146a and miR-146b differ by only two nucleotides. MiR-146a negatively regulates signal transduction pathways leading to NF-κB activation. Upon activation of a cell surface receptor such as TLR4, a molecular cascade including TRAF6 and IRAK1 leads to IκBα phosphorylation and degradation to NF-κB activation and nuclear translocation .(42) NF-κB activation induces transcription of many genes, including pri-miR-146a(42). Once translocated to the cytoplasm and loaded onto the RISC complex, mature miR-146a contributes to attenuate receptor signaling through the down-modulation of IRAK1 and TRAF6(42).TLR signaling manage regulation of miR-155,miR-146,miR-132. The targets of miR 146 are IRAK1,IRAK2 and TRAF6 and IRF5. miR-146 negatively regulates the expression of IRAK1,IRAK2,andTRAF6(42). miR-146a, miR-146b, and miR-155 downregulated in the majority of melanoma cell lines with respect to melanocytes found that ectopic expression of miR-155 in melanoma cells constrains their proliferation(43). Increasing of miR-146a/b in melanoma significantly

down regulated expression of IRAK1 and TRAF6 and negatively regulating NF-κB activity. miR-146a Exerts Differential Effects on Melanoma Growth and Metastatization. TLR4, TLR7/8 agonist-induced miR-146a promotes macrophage tolerance to MyD88-dependent TLR agonists(43). MiR-146a expression is higher in Th1 cells than in Th2 or naive T cells. MiR-146b promotes myogenic differentiation and modulates multiple genes such as HMGA2 and HMGA1 targets in muscle cells. Inhibition of endogenous miR-146b prevents the down-regulation of HMGA2 during differentiation(43).

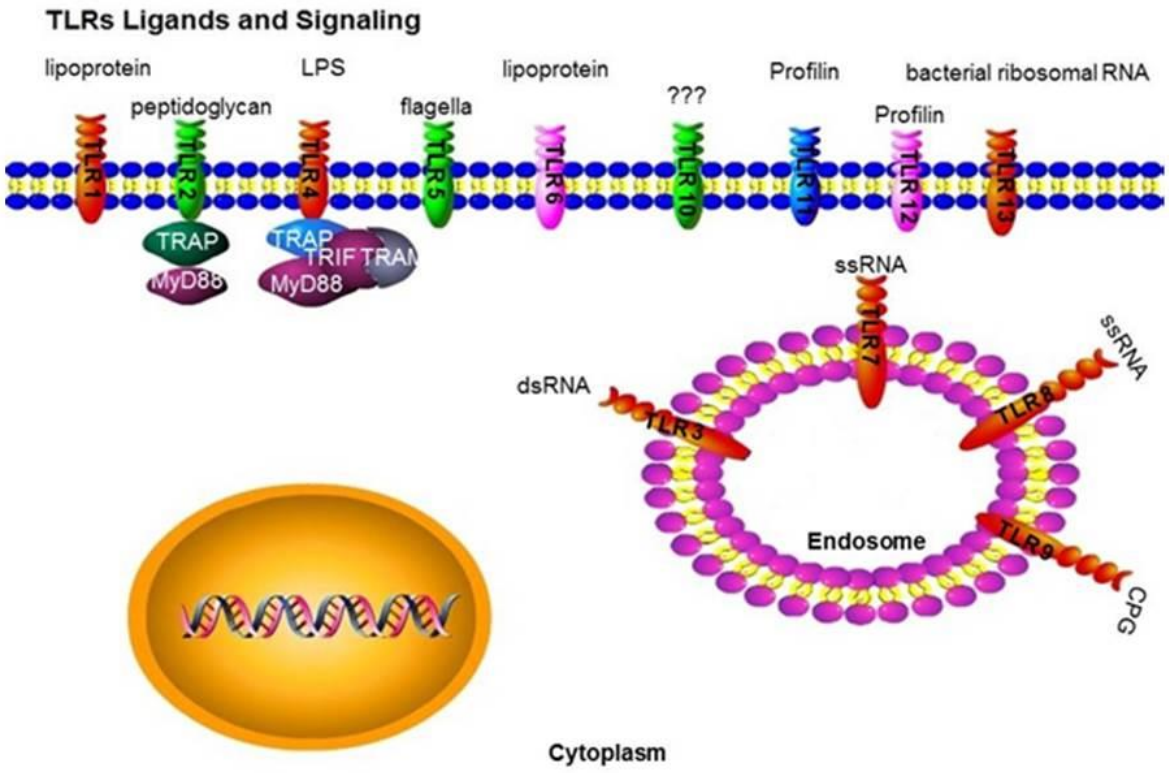

Figure 1. Summarizes the TLRs ligands and signaling

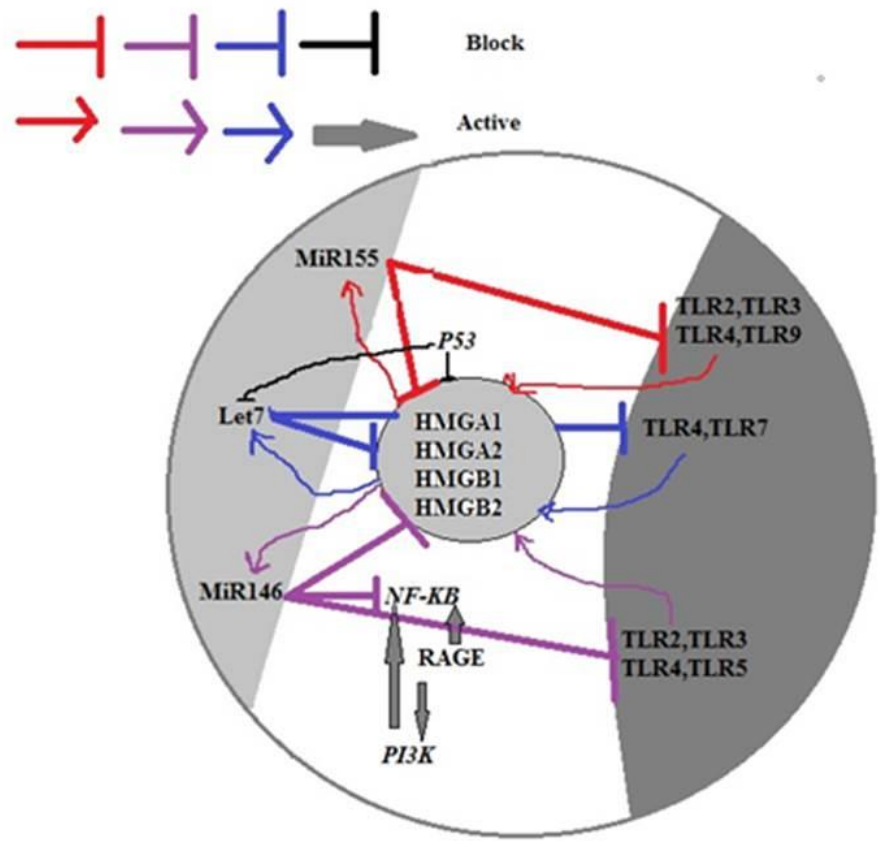

Figure 2. Summarizes the Let7 and MiR155 and MiR146 functions on TLRs and HMG groups.

Conclusion

The detection of miRNA has added a new layer of cancer therapy and will continue to increase our knowledge in this regulation. In the situation of TLRs, they are the main key to smooth initiation, resolution and control of inflammatory signals. As a present study, have an important relationship between TLRs and miRNAs with targeting of High Mobility Groups. The important notice to study in this field will include miRNA target gene-binding site knock outs which will obviously define the role of these molecules in the immune defense. The deregulation of miRNAs in immunity pathways principal to inflammation, cancerous phenotypes and many diseases clearly necessitates the research. Briefly figure 2 show the main conclusion of present review which describes the MiR146a and MiR155 and Let7 can decrease TLRs function and HMG targeting but these signaling can induce the MiRNAsin Melanoma.

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