MiRNA-146a

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miRNA-146a, a single-stranded, non-coding RNA molecule, has emerged as a valuable diagnostic and prognostic biomarker for numerous pathological conditions. Its primary function lies in regulating inflammatory processes, haemopoiesis, allergic responses, and other key aspects of the innate immune system.

miRNA immunity cancer miRNA-146a

1. Introduction

miRNAs are a class of small non-coding RNA molecules that play an essential role in regulating numerous pathways and important biological processes including innate immunity, inflammatory responses, haematopoiesis, development of malignancies and metastases. These short, single-stranded RNA molecules measure between 18–24 nucleotides in length. Their physiological role is to monitor gene expression at the post-transcriptional level by binding to the target mRNA's 3'-untranslated region. This binding can lead to the degradation of the mRNA or block its translation [1].

miRNAs play a critical role in gene regulation, affecting approximately 33% of human genes [2]. miRNAs exhibit unique patterns of modulation in inflammatory cells, cancer cells, and other cells and tissues associated with specific pathological disorders. Dysregulation of miRNAs, either up or downregulation, often leads to functional abnormalities in cellular activity.

2. MiRNA-146a—Function, Role, Involvement in Innate Immunity, Development of Inflammatory Responses, and Haematopoiesis

miRNAs play crucial roles in immune responses, supported by evidence of selective miRNA expression in immune cells [3]. miRNA-146a is located on chromosome 5 and has been extensively studied. Knocking out miRNA-146a in mice resulted in autoimmunity, increased sensitivity to lipopolysaccharides (LPS), and heightened pro-inflammatory activity upon endotoxin exposure. Additionally, miRNA-146a deficiency in mice led to age-related tumour formation and myeloproliferation, suggesting its role in regulating immune cell proliferation [4]. This implied that miRNA-146a is essential for transmitting nuclear factor kappa B (NF-κB) signals, and its absence contributed to myeloid

malignancies [5]. Similarly, miRNA-146a-deficient mice mimic myelodysplastic syndrome (MDS) patients with fifth chromosome deletion.

Toll-like receptors (TLRs) are crucial for innate immunity as they recognize microbial structures and initiate immune responses. Humans have 11 TLRs (TLR-1 to TLR-11), expressed in different cell types, capable of binding various ligands [6]. TLRs activate the innate immune response through the MyD88 signalling pathway or TRIF signalling pathway. miRNA-146a targets key signalling proteins in the MyD88-dependent pathway, demonstrating its significance in innate immunity (**Figure 1**).

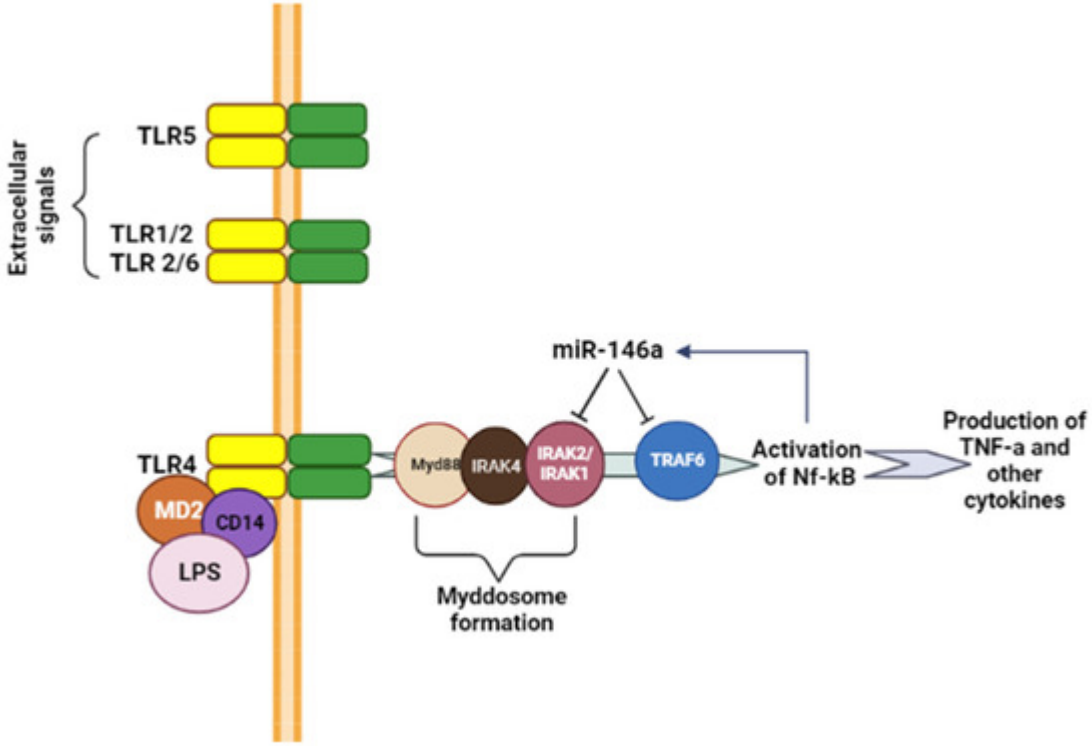

Figure 1. miRNA-146a targets involved in the MyD88-dependent signalling pathway.

Adapter molecules activate downstream transcription factors, including NF-κB, mitogen-activated protein kinase (MAPK), interferon regulatory factor family members (such as IRF3 and IRF7), and activator protein-1 (AP-1), which induce proinflammatory cytokines, type 1 interferons (IFNs), and antiviral proteins [7]. Most TLRs use the MyD88 pathway, which activates NF-κB and MAPK, except for TLR3, which can activate the TRIF signalling pathway [8]. Sufficient TLR signalling is necessary to effectively kill the pathogen, but an uncontrolled TLR reaction can harm the host. Thus, the TLR-mediated inflammatory response should be supervised, and the complex regulatory potential provided by miRNAs, especially miRNA-146a, is crucial for the physiological functioning of this type of innate immune response.

miRNA-146a targets adapter proteins interleukin-1 receptor-associated kinase 1 (*IRAK1*; kinase associated with the IL-1 receptor 1) and *TRAF6* (factor associated with the TNF receptor 6) involved in TLR and IL-1 receptors

signalling, inhibiting proinflammatory mediator secretion, and blocking TLR signals [9]. This suggests that targeting adapter molecules with miRNA-146a might regulate TLR-mediated innate immunity [9].

According to the literature, miRNA-146a plays an important role in endotoxin-induced tolerance [10]. This mechanism decreases monocyte responsiveness to LPS after prolonged or repeated exposure, preventing inflammation from continuous contact with bacterial components. LPS exposure increases miRNA-146a levels in THP-1 cells (a human leukaemia monocytic cell line), which negatively correlates with TNF levels, indicating tolerance to LPS [10]. Positive miRNA-146a regulation is necessary for tolerance activation, and exogenous miRNA-146a transfection induces tolerance even without LPS priming, while miRNA-146a knockdown reduces tolerance to LPS [11]. miRNA-146a also contributes to innate immune tolerance in new-borns' intestines, preventing intestinal epithelial cell apoptosis upon bacteria exposure [12]. These studies indicate that although miRNA-146a is induced by TLR signalling, its primary role may be to serve as a dominant regulator of negative feedback to prevent uncontrolled inflammation resulting from prolonged contact with bacterial agents.

miRNA-146a is extensively studied in inflammation and immunity, acting as a dominant negative feedback regulator in vertebrate innate immune responses. Mechanistically, miRNA-146a targets key components of the MyD88-dependent signalling pathway, such as IRAK1 and TRAF6, leading to a coordinated decrease in the synthesis of various inflammatory mediators. Although most of the research has focused on the TLR pathway and inflammatory cells, miRNA-146a is expressed in various other cell types and may participate in other functions depending on the context (**Figure 2**).

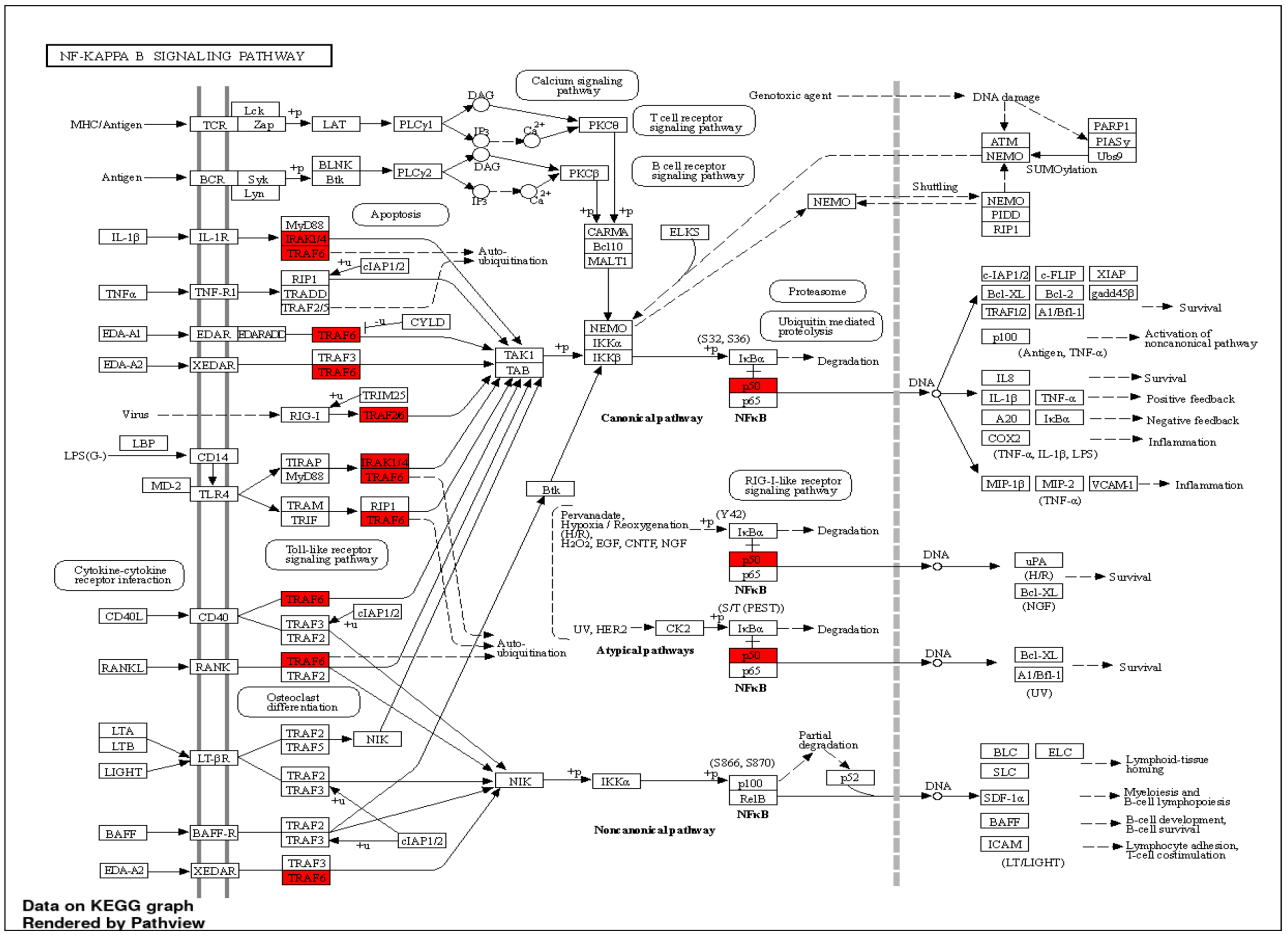

Figure 2. Target genes of miRNA-146a validated for the TLR signalling pathway (indicated in red), based on the KEGG database.

In haematopoiesis, miRNA-146a plays a vital role, regulating target gene expression and contributing to certain hematopoietic diseases. It is predominantly expressed in multipotent stem cells, granulocytic/monocytic progenitors, megakaryocytic/erythroid progenitors, and myeloid progenitors. Overexpressing miRNA-146a in hematopoietic bone marrow stem cells increases granulocytes and red blood cells but worsens lymphopoiesis. Forced miRNA-146a expression impairs bone marrow repair [13]. Healthy individuals show high miRNA-146a expression in bone marrow CD34 precursors, but patients with acute myeloid leukaemia have lower levels, particularly in monocytes, granulocytes, erythrocytes, and megakaryocytes from both peripheral blood and bone marrow of healthy donors [14]. Differentiation of the acute promyelocytic leukaemia cell line NB4 leads to decreased miRNA-146a expression upon trans-retinoic acid induction [15]. However, miRNA-146a is actively expressed in regulatory T cells and type 1 T helper cells compared to mature T cells and type 2 T helper cells. miRNA-146a expression in megakaryocytes varies across different experiments [16][17][18]. The role of miRNA-146a in megakaryocyte development warrants further investigation, considering its diverse effects in different experimental contexts.

miRNA-146a targets *TRAF6* and *IRAK1* genes, leading to increased protein expression in knockout cell lines. *TRAF6* is involved in myeloid cells development, and overexpression associates with acute myeloid leukaemia

growth, suggesting that miRNA-146a acts as a tumour suppressor gene. Mice without miRNA-146a expression develop tumours in lymphoid organs, indicating its inhibition promote tumour growth and metastasis. However, miRNA-146a deficiency alone is not sufficient for oncogenesis, indicating that other factors interact with malignant tumour development [19]. Chromosomal translocations and gene mutations in acute myeloid leukaemia (AML) associate with miRNA-146a expression [20]. Recently, an increasing number of studies have proven that microRNA expression can influence the clinical outcome of AML. In particular, a study by Zhang et al. [21] indicates that miRNA-146a is highly expressed in both acute lymphoblastic leukaemias (ALL) and AML in children. Given its ability to regulate gene expression, miRNA-146a may serve as a diagnostic and prognostic marker for hematopoietic diseases. In addition, targeting miRNA-146a expression may be a potential therapeutic strategy for controlling leukemogenesis. Overall, the study of miRNA-146a expression advances the understanding of the molecular mechanisms underlying normal and abnormal haematopoiesis.

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