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Cellular Signalling 20 (2008) 269–276
CELLULAR SIGNALLING
www.elsevier.com/locate/cellsig

Review

IRAK1: A critical signaling mediator of innate immunity

Sridevi Gottipati, Navin L. Rao, Wai-Ping Fung-Leung *

Immunology, Johnson & Johnson Pharmaceutical Research and Development, L.L.C., San Diego, CA 92121, USA

Received 3 August 2007; accepted 14 August 2007
Available online 23 August 2007

Abstract

The innate immune system is equipped with sensitive and efficient machineries to provide an immediate, first line defense against infections. Toll-like receptors (TLRs) detect pathogens and the IL-1 receptor (IL-1R) family enables cells to quickly respond to inflammatory cytokines by mounting an efficient protective response. Interleukin-1 receptor activated kinases (IRAKs) are key mediators in the signaling pathways of TLRs/IL-1Rs. By means of their kinase and adaptor functions, IRAKs initiate a cascade of signaling events eventually leading to induction of inflammatory target gene expression. Due to this pivotal role, IRAK function is also highly regulated via multiple mechanisms. In this review, we focus on IRAK1, the earliest known and yet the most interesting member of this family. An overview on its structure, function and biology is given, with emphasis on the different novel mechanisms that regulate IRAK1 function. We also highlight several unresolved questions in this field and evaluate the potential of IRAK1 as a target for therapeutic intervention.

Keywords: IRAK; IL-1; TLR; IL-1R; IL-18; IL-33; Splice variant; Signal transduction; Kinase; Adaptor protein; Phosphorylation; Ubiquitination; Protein degradation; Autoimmune disease; Endotoxin tolerance

Contents

1. Introduction

Interleukin-1 receptor-associated kinases (IRAKs) are a unique family of death domain containing protein kinases that play a key role in the signaling cascades of two receptor families, Toll-like receptors (TLRs) and interleukin-1 receptors

* Corresponding author. Rm 2608, Immunology Team, Johnson & Johnson Pharmaceutical Research and Development, 3210, Merryfield Row, San Diego, CA 92121, USA. Tel.: +1 858 450 2016; fax: +1 858 450 2081.
E-mail address: wleung@prdus.jnj.com (W.-P. Fung-Leung).

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doi:10.1016/j.cellsig.2007.08.009

(IL-1Rs). TLRs are pathogen recognition receptors responsible for mounting the initial response to infections. IL-1R and its family members, such as IL-18R and IL-33R, are cytokine receptors that initiate and modulate inflammatory and immune responses. Unregulated TLR or IL-1R activation may lead to pathological situations ranging from chronic inflammation to the onset of autoimmune diseases. Different attempts have been made to modulate TLR/IL-1R responses, such as directly blocking receptor activation or inhibiting downstream signaling pathways. Inhibition of IRAK function may be an effective approach in blocking the common, pro-inflammatory signaling pathways shared by both TLRs and IL-1Rs.

There are four mammalian members in the IRAK family: IRAK1, IRAK2, IRAK3 (IRAKM) and IRAK4. Although IRAKs are categorized as serine/threonine protein kinases and all contain a kinase-like domain, only IRAK1 and IRAK4 exhibit kinase activity [1,2]. IRAK1 is the first member of this kinase family that was identified as a key component of the IL-1R signaling pathway. The *Drosophila* orthologue of IRAK1, Pelle, is involved in signaling downstream of the Toll–Dorsal pathway during embryonic development. While several recent publications have given comprehensive reviews on the IRAK family [3–5], IRAK1 will be the main focus of discussion in this review.

2. The IRAK1 gene and protein

The IRAK1 gene is composed of 14 exons and is located on the X chromosome [6]. IRAK1 variants from alternative splicing have been identified [7,8] and their potential role will be discussed below. The IRAK1 protein contains an N-terminal death domain (amino acid residues 1–103 in human IRAK1), an undefined domain (residues 104–198), a central kinase domain (residues 199–522) with an activation loop (residues 364–388), and the C-terminal C1 and C2 domains (residues 523–618 and 619–712, respectively) (Fig. 1). Although other IRAK members also share similar functional domains, the overall sequence homology among the four family members is only 30–40%. IRAK1 and other members are ubiquitously expressed, with the exception of IRAKM, which is detected only in macrophages in an inducible manner [1,9]. While a crystal structure of IRAK4 has been reported, an IRAK1 structure has not been resolved [10].

3. The role of IRAK1 in IL-1R, IL-18R and IL33-R biology

IL-1α and IL-1β, collectively referred to as IL-1, are cytokines with pleiotropic effects in inflammation. IL-1 induces a wide variety of inflammatory mediators including IL-6 and tumor necrosis factor (TNF)-α. Due to the potent pro-inflammatory effects of IL-1, the IL-1R is regulated by multiple mechanisms, including the decoy receptor IL-1R2, the natural antagonist IL-1Ra, and splice variants of IL-1 and its receptor. IL-1R is composed of two subunits, IL-1R1 and IL-1RAcP, which are ubiquitously expressed. In fibroblasts, IL-1R activation leads to the enhanced IL-6 production in an IRAK1-dependent manner. IRAK1-deficient fibroblasts produce significantly reduced levels of IL-6 in response to IL-1 stimulation [11].

IL-18R is a member of the IL-1R family and is composed of IL-18Ra and IL-18Rb (also known as IL-1Rrp1 and IL-1AcPL, respectively). The IL-18 response is modulated by IL-18 binding protein (IL-18BP) that functions as a negative regulator. IL-18R expression is restricted to natural killer (NK) cells and type 1-helper (Th1) T cells [12,13]. Th1 cells derived from IRAK1-deficient mice are defective in interferon (IFN)-γ production upon IL-18 stimulation [14]. NK cells isolated from cytomegalovirus-infected IRAK1 knockout mice also produce significantly reduced levels of IFN-γ, yet retain normal NK cytotoxicity [14].

IL-33R, also known as ST2, is another IL-1R member and its activating ligand, IL-33, is known as IL-1F11. In contrast to IL-18R, IL-33R is primarily expressed on mast cells and type 2-helper (Th2) T cells, and is functionally linked to Th2 immune responses [15,16]. IL-33-treatment of Th2 T cells induces IL-5 and IL-13 production [15]. Mice injected with IL-33 develop splenomegaly, eosinophilia and elevated serum IgE levels. Pathological changes in the lung and digestive tract are also observed in these mice [15]. Although IRAK1 is recruited to the activated IL-33R, the importance of IRAK1 in mediating IL-33R function has not been studied. While several new members of IL-1 and its receptor family have recently been described

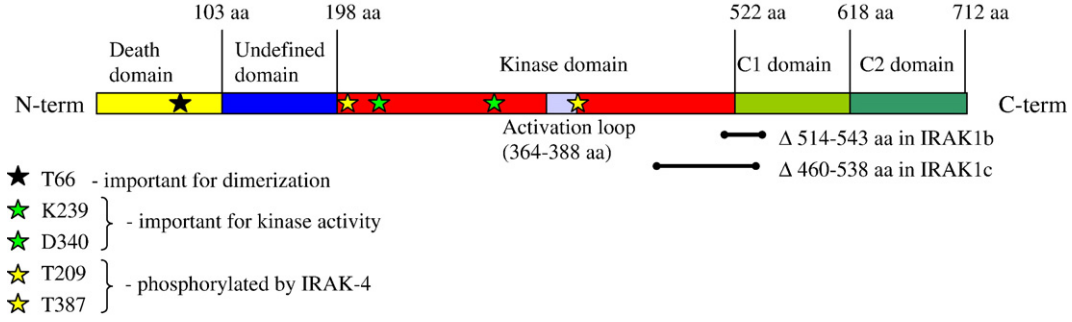

Fig. 1. Functional Domains of IRAK1: IRAK1 is composed of an N-terminal death domain, a kinase domain with an activation loop, and the C-terminal C1 and C2 domains. The region between the death and kinase domains is yet to be defined. The key residues in the structure are highlighted by the star symbols. The solid star indicates Thr-66 in the death domain that is important for oligomerization. The two green stars indicate Lys-239 and Asp-340 in the kinase domain that are critical for the kinase function of IRAK1. The two yellow stars are Thr-209 and Thr-387 in kinase domain that are phosphorylated by IRAK4. The two splice variants of the human IRAK1 are also highlighted in the figure. The deletion (Δ) of 514–543 or 460–538 amino acids results in splice variants IRAK1b or IRAK1c, respectively.