Journal of Dermatological Science (2005) 39, 71—80

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Journal of Dermatological SCIENCE

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REVIEW ARTICLE

The cytosolic pattern-recognition receptor Nod2 and inflammatory granulomatous disorders

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Received 4 February 2005; received in revised form 12 April 2005; accepted 14 April 2005

KEYWORDS
Blau syndrome;
Crohn's disease;
Early-onset sarcoidosis;
Nod2;
Toll-like receptor

Summary Pattern-recognition receptors are a first line of defense against invading pathogens. Recent advances in the understanding of innate immunity have revealed a novel family of cytosolic pattern-recognition receptors called Nods, which contain an amino-terminal effector-binding domain, a centrally located nucleotide-binding oligomerization domain (NOD) and a carboxy-terminal ligand recognition domain. Hereditary mutations of Nods have been reported in patients with certain inflammatory diseases; for example, Nod2 mutations are associated with the inflammatory granulomatous disorders, Crohn's disease and Blau syndrome. Missense mutations of Nod2 are also associated with early-onset sarcoidosis, a rare but sporadic disease. Because Nod2 is predominantly expressed in monocytes and recognizes a component of bacterial peptidoglycan, analysis of its function may help in understanding the role of the immune system in granuloma formation.

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Abbreviations: Apaf-1, apoptotic protease activating factor 1; CARD, caspase-recruitment domain; IL-1β, interleukin 1β; LPS, lipopolysaccharide; MDP, muramyl-dipeptide; NF-κB, nuclear factor κB; NOD, nucleotide-binding oligomerization domain; PYD, pyrin domain; R genes, disease-resistance genes; Th1, T helper type 1; TIR, Toll/IL-1 receptor like domain

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0923-1811/$30.00
doi:10.1016/j.jdermsci.2005.04.001

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1. Introduction

The immune system can be divided into two major branches: innate immunity and adaptive immunity. In adaptive immunity, invading pathogens are recognized as peptide antigens by antigen receptors expressed on the surfaces of B and T cells. To detect a wide range of potential antigens, B and T cells must rearrange their immunoglobulin and T cell receptor genes. In contrast, innate immunity provides the initial line of defense against invading pathogens and relies on germ line-encoded receptors that recognize the structure of pathogen-associated molecular patterns. Because the structure of each pathogen-associated molecular pattern is highly conserved, detection of most or all microbial agents can be mediated by a surprisingly small number of specific host pattern-recognition receptors.

One well-characterized family of pattern-recognition receptors comprises the type I transmembrane signaling receptors known as Toll-like receptors [1,2]. Toll-like receptors contain extracellular domains composed of leucine-rich repeats that recognize pathogen-associated molecular patterns; the recognition events result in the transduction of signals into the interior of host cells (Fig. 1). These signals mediate host immune responses by inducing the secretion of several pro-inflammatory cytokines and co-stimulatory cell-surface molecules through the activation of transcription factors, including nuclear factor-κB (NF-κB).

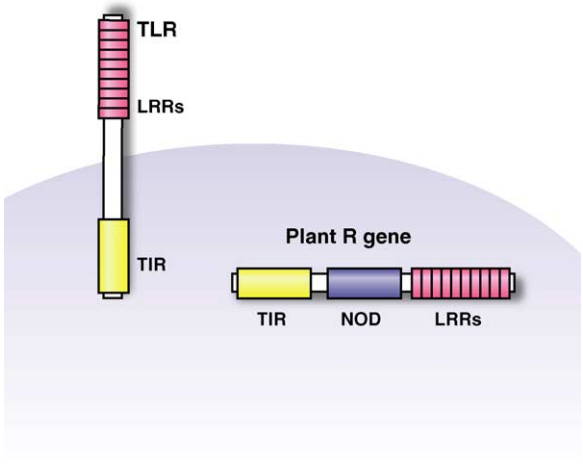

Fig. 1 Toll-like receptor (TLR) and plant disease-resistance (R) gene. Toll-like receptor contains leucine-rich repeats (LRRs) in an extracellular domain, whereas the plant R gene is a cytosolic pattern-recognition receptor. TIR: Toll/IL-1 receptor like domain.

2. The Nods family of cytosolic pattern-recognition receptors

A recently identified family of cytosolic proteins containing leucine-rich repeats also appears to take part in innate immunity [3]. In addition to leucine-rich repeats, many of these proteins contain a predicted nucleotide-binding fold, known as the nucleotide-binding oligomerization domain (NOD). The NOD-related proteins are referred to as Nods.

The first Nod to be described was apoptotic protease activating factor 1 (Apaf-1), which is an essential regulator of programmed cell death (Fig. 2a). In nematodes, the expression of the Apaf-1 homologue CED-4 is required for the suicide program. Apaf-1 contains an amino-terminal caspase-recruitment domain (CARD), followed by a NOD that mediates self-oligomerization and a car-

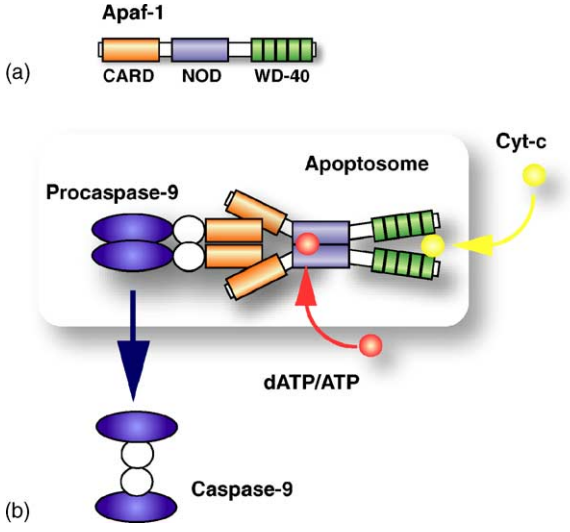

Fig. 2 Apoptotic protease activating factor 1 (Apaf-1). (a) Apaf-1 contains an amino-terminal caspase recruitment domain (CARD), a centrally located nucleotide-binding oligomerization domain (NOD), and a carboxy-terminal WD-40 repeat. (b) Apaf-1 assembles a multicomponent complex called the apoptosome using its protein/protein interaction domain, resulting in the activation of caspase 9. Cyt-c: Cytochrome *c*.