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The CATERPILLER family: An ancient family of immune/apoptotic proteins

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Abstract

Ancient immune pathways in other species have provided clues for the discovery of important molecules in the mammalian immune system. A notable example is the discovery of Toll-like receptors based on the Toll receptors in *Drosophila*. In plants, a subclass of the disease resistance (*R*) genes is crucial for immune defense against a host of insults. This *R* gene subclass encodes a combined nucleotide-binding domain/leucine rich region (NBD/LRR) motif. Intriguingly, proteins with such a motif are found in mammalians, and several are also shown to be important in inflammatory and immune responses. This family, which we designated as the CATERPILLER (CARD, Transcription Enhancer, R (purine)-binding, Pyrin, Lots of Leucine Repeats) gene family while others have designated it as the NOD family, has over 20 members. They are crucial in the control of cytokines, inflammatory responses, NF-?B activation, and likely cell death and survival. Several prominent members including CIITA, CIAS1, and NOD2 are linked to immunologic genetic disorders that are hereditary. This indicates that these genes are ancient and important regulators of the immune system.

Keywords: Innate immunity; CATERPILLER; NOD; Plant *R* genes

Identification of the CATERPILLER gene family

The identification of the CATERPILLER (CARD, Transcription Enhancer, R(purine)-binding, Pyrin, Lots of Leucine Repeats) gene family (CLR) [1,2] was initiated because of our longstanding interest in the class II transactivator (*CIITA*) (Fig. 1) [3]. *CIITA* is the master transcriptional regulator of classical and nonclassical MHC-II genes and the invariant chain gene (Ii) [3,4]. *CIITA* contains a nucleotide-binding domain (NBD) [5] and a C-terminal leucine rich region (LRR) [6,7], both of which are important for its function as a trans-activator. The NBD contained in CIITA appears to be a GTP-binding motif [8,9], while the LRR is similar to that found in ribonuclease [10]. The NBD and LRR domains serve as dimerization domains and are proposed to serve to enhance both dimerization among similar domains (e.g., LRR to LRR) and among dissimilar domains (LRR to NBD) [6,7,11–13].

CIITA appears to be a distant cousin of a well-known protein, *Apaf-1* (apoptotic protease-activating factor-1) [7]. *Apaf-1* is a mammalian homologue of the CED-4 protein found in *Caenorhabditis elegans*, which is essential for apoptosis in these nematodes [14]. Apaf-1 contains a CARD (caspase activation and recruitment domain) [15] as well as an ATP-binding domain [16]. Apaf-1 is activated when cytochrome *c* is released from the mitochondria into the cytoplasm during apoptosis. Activation of Apaf-1 induces the oligomerization of Apaf-1 to form a large caspase-activating complex, leading to caspase-9 activation and cell death [17]. When the NOD1 (nucleotide oligomerization domain) and NOD2 proteins were discovered, these proteins

Abbreviations: NBD, nucleotide binding domain; LRR, leucine rich repeat; CARD, caspase recruitment domain; CATERPILLER, CARD, Transcription Enhancer, R(purine)-binding, Pyrin, Lots of Leucine Repeats; TLR, Toll-like receptor; NOD, (nucleotide oligomerization domain).

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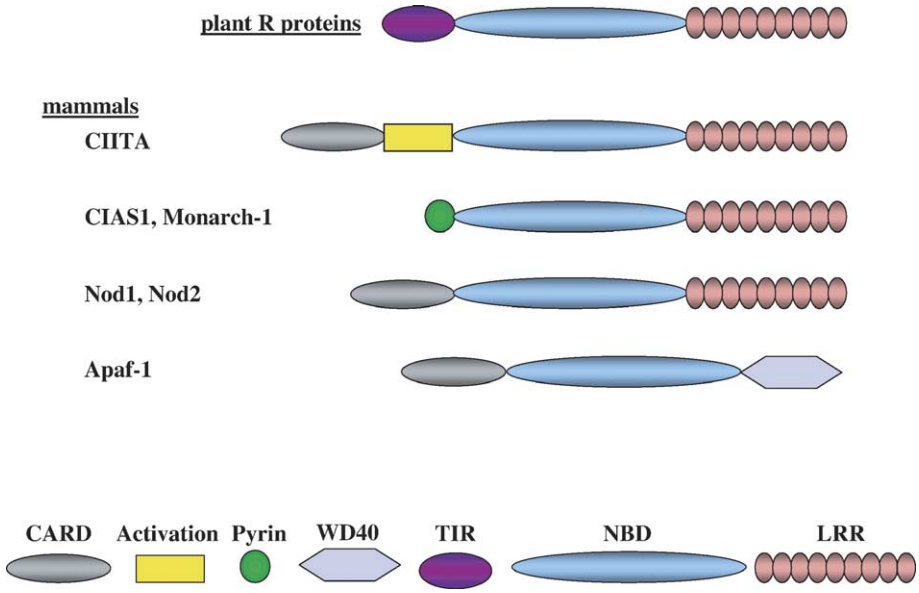

Fig. 1. Domain structure of the CATERPILLER family and associated proteins. Apaf-1 and R proteins are shown as related proteins. Pyrin, Pyrin domain; CARD, caspase-recruitment domain; Activation, Activation domain; TIR, Toll-IL-1 receptor domain; NBD, nucleotide-binding domain; LRR, leucine-rich repeat; WD40, WD40 repeat region.

were found to be similar to Apaf-1 in that they contain an N-terminal CARD domain, and a mid-nucleotide binding domain [18,19]. The C-termini of both proteins consist of LRRs. Based on sequence analysis, it was noted that the NOD proteins also shared structural similarity with CIITA [7]. Subsequently, we searched for genes that share a similar NBD/LRR domain structure to *CIITA*. Using the NBD and LRR as BLAST baits, we first found more than 20 known and novel family members by a search of the public and private genomic databases [1]. We named these genes the CATERPILLER family of genes characterized by the NBD/LRR motifs in the C-terminal two thirds of their sequences. Aside from *NOD1/NOD2* [19–22] and the more distant relative, *Apaf-1* [23], some of the known genes in this family included the NAIP (neuronal apoptosis inhibitory protein) [24,25] linked to the inhibition of apoptosis and CIAS1 (the cold-induced autoinflammatory syndrome) [26] linked to several autoinflammatory syndromes. Thus, it is predicted that this family is likely to play an important role in the control of inflammation, immune response and cell death.

Ancient immune systems in plants also have NBD/LRR motifs

It is important to note that the combinatory motifs of NBD/LRR are present in plant signaling proteins that induce gene expression and cell death in response to pathogen infections [27,28]. In plants, proteins bearing the NBD/LRR motifs are the major class of disease resistance mediators, called R proteins. The R proteins form an ancient immune system that is pivotal for the survival of plants against an array of pathogens. The R proteins are important for the defense of plants against viruses, bacteria, fungi, nematodes, and even insecticides. In plants, the N-termini and are comprised of coiled-coil structures or TLR-IL-1R (TIR) domains [27,28]. In mammals, CATERPILLER proteins are also linked to a limited number of distinct N-terminal domains [1]. Most have a pyrin domain, which bears similarity to other death domains. Other N-terminal domains include the CARD domain or the activation domain.

The association of CATERPILLER genes with immune disorders

One of the most intriguing features of CATERPILLER genes that provide clues to their function is their association with a variety of inherited immunologic disorders. *CIITA* is the master regulator of MHC-II genes [29–32], and genetic lesions in this gene result in the loss or reduction of MHC-II expression. The lack of MHC-II expression leads to an immunodeficiency disorder known as Type II Bare Lymphocyte Syndrome (BLS) (Group A). Mutations in *NOD2/CARD15* have been associated with increased susceptibility to irritable bowel disease, Crohn's disease, and a granulomatous disorder known as Blau syndrome [22,33–35]. Mutations in the *CIAS1* gene predispose patients to three autoinflammatory disorders [26,36–39]. Mutations in *CIAS1* have been segregated in family members affected with the familial cold urticaria (FCU) syndrome, Muckle-Wells syndrome (MWS) and the neonatal-onset multisystem inflammatory disease (NOMID), also known as chronic infantile neurologic cutaneous articular (CINCA) syndrome. All three of these diseases are characterized as having an inflammatory component. Although the mecha-