Insect immunology and hematopoiesis

The most encompassing physical barrier of insects is the cuticle. This chitinous, hydrophobic material forms the exoskeleton, and also lines foregut, hindgut and tracheal system. Pathogens enter body through cuticle via wound or enzymatic digestion. Ingestion is another routine for pathogen entrance.

Multiple insect cells and tissues are involved in immunity. Hemocytes are the primary immune cells. They circulate with hemolymph (circulating hemocytes) or attach to tissues (sessile hemocytes). These cells drive cellular and humoral immunity. Fat body is composed of loosely associated cells that are rich in lipids and glycogen, lines the integument of hemocoel. It functions in energy storage and synthesis of vitellogenin precursors that are required for egg production. Fat body also produces antimicrobial peptide. Midgut mainly functions in digestion and nutrition absorption. It produces nitric oxide synthesis and other lytic effectors killing pathogens. Salivary glands are primarily involved in feeding and usually located in the anterior of thorax. It is involved in immunity.

1 Pattern recognition receptors (PRRs)

Immune responses are initiated by recognition of pathogen-associated molecular patterns (PAMPs) by pattern recognition receptors (PRRs). Among PRR families are

(1) PGRPs: peptidoglycan recognition proteins;

(2) immunoglobulin domain proteins;

(3) FREPs: fibrinogen-related proteins, also known as fibrinogen domain immunolectins (FBNs);

(4) TEPs: thioester-containing proteins;

(5) betaGRP: beta-1,3-recognition proteins, also known as Gram-negative bacterial-binding proteins (GNBPs);

(6) galectins: bind specifically to beta-galactoside sugars;

(7) CTLs: C-type lectins;

(8) leucin-rich repeat (LRR) containing proteins;

(9) DSCAMs: down syndrome cell adhesion molecules;

(10) Nimrod proteins;

(11) MLs: MD-2-like proteins, also known as Niemann-pick type C-2 proteins, possess myeloid-differentiation-2-related lipid-recognition domains involved in recognizing lipopolysaccharide.

2 Toll signaling

Toll pathway functions in both development and immunity. In immunity, Toll signaling is initiated when PRR activates

(1) SPZ: Spaetzle, extracellular cytokine;

SPZ binds cellular receptor

(2) TLR: toll-like receptors, also known as Toll.

TLR activates downstream cascade including

(3) MyD88: myeloid differentiation primary response 88;

(4) Tube;

(5) Pelle, orthologous to several human genes including interleukin 1 receptor associated kinase 1 (IRAK1);

(6) Dorsal, orthologous to several human genes including RELA (RELA proto-oncogene, NF-kappaB subunit) and RELB (RELB proto-oncogene, NF-kappaB subunit);

(7) Dif:Dorsal-related immune factor, orthologous to several human genes including RELA (RELA proto-oncogene, NF-kB subunit) and RELB (RELB proto-oncogene, NF-kB subunit).

The inhibitor of Toll signaling is

(8) Cactus orthologous to several human genes including NF-kappaB inhibitor alpha (NFKBIA);

Toll signaling is effective in combating Gram-positive bacteria, fungi and viruses.

3 Imd Signaling

Imd signaling is activated by membrane receptor PGRP-LC, followed by intracellular signaling including

(1) Imd: immune deficiency;

(2) TAK1: transforming growth factor (TGF)-beta activated kinase 1, orthologous to human mitogen-activated protein kinase kinase kinase 7 (MAP3K7);

(3) IKKgamma: inhibitor of NF-kappaB (IkappaB) kinase gamma, also known as Kenny in *Drosophila melanogaster*, orthologous to human IKKgamma and optineurin;

(4) IKKbeta: IkappaB kinase beta;

(5) Fadd: fas-associated death domain;

(6) Dredd: death-related ced3/Nedd2-like caspase, orthologous to several human genes including caspase 10;

and finally activates NF-kappaB transcription factor

(7) Relish, orthologous to several human genes including NFKB2 (nuclear factor kappa B subunit 2).

The inhibitor of Imd signaling is

(8) Caspar, orthologous to human fas-associated factor 1 (FAF1).

Imd signaling is effective in combating Gram-negative bacteria and viruses.

4 JAK/STAT signaling

JAK/STAT signaling functions in development and immunity. In immunity, JAK/STAT signaling begins with extracellular cytokine

(1) Unpaired

that activates

(2) Domeless.

Domeless is phosphorylated by

(3) Hopscotch: orthologous to several human genes including JAK1 (Janus kinase 1) and JAK3 (Janus kinase 3).

Hopscotch activates transcription factor activity of

(4) Stat: signal transducer and activator of transcription protein.

Inhibitors of JAK/STAT signaling are

(5) Socs: suppressor of cytokine signaling;

(6) Pias: protein inhibitor of activated Stat, known as suppressor of variegation 2-10 (Su(var)2-10) in *Drosophila melanogaster*.

JAK/STAT signaling activates antimicrobial genes like nitric oxide synthase and functions in antibacterial and antiviral responses.

Phagocytosis

Phagocytosis is a rapid progress conducted by hemocytes. PRRs that have been shown to be involved in phagocytosis include TEPs, Nimrods, DSCAMs, beta-integrins and PGRPs. The intracelular signaling in phagocytosis remains poorly understood. In mosquitoes,

(1) CED2: cell death abnormal 2;

(2) CED5;

(3) CED6

are involved in signaling regulate internalization of bacteria (Moita *et al.*, 2005).

Melanization

Melanization is an enzymatic process involved in cuticle hardening, egg chorion tanning, wound healing and immunity. In immunity, melanization functions in killing bacteria, fungi, protozoa parasites, nematode worms and parasitoid wasps. Melanin synthesis pathway includes:

(1) PAH: phenylalanine hydroxylase, also known as phenylalanine 4-monooxygenase, hydroxylates phenylalanine to tyrosine;

(2) PO: phenoloxidase, oxidizes tyrosine into dihydroxyphenylalanine (Dopa), and further into dopaquinone, and further into dopachrome non-enzymatically;

(3) DCE: dopachrome conversion enzyme, decarboxylates dopachrome into 5,6-dihyroxyindole (DHI).

Another line from Dopa to DHI is

(4) DDC: dopa decarboxylase, decarboxylates dopa into dopamine, which is oixidized into dopaminequinone by PO, and further converts into dopaminechrome non-enzymatically, and further into DHI non-enzymatically.

Following PO-meidated DHI oxidation, indole-5,6-quinones polymerize and give rise to heteropolymer eumelanin. PO activity is tightly controlled. After PRR activation, PO is activated by a serine protease cascade including:

(5) ModSp: modular serine proteinase that lacks clip domain but contains other domain for interactions;

(6) cSP: clip domain-containing serine protease, activated by ModSp cleavage and activates PO by cleavage.

The inhibitor of PO is

(7) serpin: a family of serine proteinase inhibitors.

Encapsulation