Biological Forum – An International Journal **14(4): 348-352(2022)**

ISSN No. (Print): 0975-1130
ISSN No. (Online): 2249-3239

Studies of Immune Responses in Silkworm *Bombyx mori* L.: A Review

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(Received 19 August 2022, Accepted 05 October, 2022)
(Published by Research Trend, Website: www.researchtrend.net)

ABSTRACT: *Bombyx mori* L. is one of the most important sericigenous insect commercially reared for silk production. Similar to other insects, silkworm is also susceptible to a wide range of pathogens. The resistance or susceptibility to pathogens in silkworm is dependent on the genetic constitution of the host which represents the immunity of an organism towards pathogens. The innate immune responses of silkworm constitute both cellular and humoral reactions including synthesis and release of antimicrobial peptides for inhibition and elimination of foreign agents. All the immune reactions in silkworms functions by means of either Toll and Immunodeficiency signaling pathway pathways or participation of Janus Kinase / Signal Transducer and Activator of Transcription signaling pathway which works subsequently for particular pathogen type. This short review highlights studies that have contributed to our understanding of silkworm immune response against pathogens.

Keywords: Humoral, cellular, antimicrobial, peptides, pathogens, Signal, Transducer.

INTRODUCTION

Silkworm *Bombyx mori* L. is one of the most important monophagous sericigenous insect belonging to the family Bombycidae and order Lepidoptera, generally domesticated for silk production (Chanotra *et al.,* 2022). Despite the fact being the second largest producer of raw silk after China, Indian sericulture industry encounters several limitations serves as obstacles in exploring the full potential of the country (Jaydeb *et al.,* 2000; Nagaraju, 2008; Bhat *et al.,* 2022). One of the major limiting factors responsible in crop loss in sericulture industry is the outbreak of diseases and fluctuations in environmental factors which results in crop failure and thus the industry faces huge economic loss (Chanotra and Angotra 2022; Garg 2022). Silkworm similar to other living insects serves as a suitable host system for various infectious and disease causing pathogens. Susceptibility or resistance of any silkworm breed, race or hybrid against any disease causing pathogen can be attributed entirely to it genetic constitution or gene pool which collectively constitutes the immune system or immunity of the insect. The immune potential of any silkworm breed is demarked by the inherent immune reactions produced by the host against the invading pathogen.

Immunity or the defense system can be broadly defined as the ability of an organism offering resistance against specific pathogen so as to escape from the disease incidence. Immune system can be broadly viewed as an interconnected and interrelated series of cells, tissues and organs participating subsequent functions to provide resistance to the host against the invading pathogens (Anonymous, 2003). Immune system generally offers three different levels of protection namely;

1. Physical Barriers: e.g. Skin, mucous membranes, tears and saliva etc.
2. Innate (non-specific) immunity e.g. Phagocytosis and Antimicrobial proteins
3. Adaptive (specific) immunity e.g. B-cells and T-cells and Antibodies, Cytokines etc. Majority of the insects including *Bombyx mori* L. are believed to possess innate immunity and further insect immune responses are categorized into two important categories i.e. celluar and humoral immune responses (Tanaka *et al*., 2011). Insects utilize the strength of both physical barriers in the form of integument and peritropic membrane to offer resistance against the pathogens (Chen *et al.,* 2018). Integument resists the entry of disease causing agents (Ashida and Brey 1995; St Leger, 1991) and peritropic membrane on the other hand prevents host gut tissue to be damaged by the

pathogen thus serves as first line of defense in most of the insects including silkworm (Bulet *et al.,* 1999 and Wu *et al.,* 2016). In silkworm, activation and expression of various immune responses and their reaction towards the foreign pathogens imparts considerable resistance to the breed and it can be more pronounced by the collective action of cellular and humoral responses (Table 1). Therefore, in order to understand the complexity of insect immune system and their actions in majority of the insect including silkworm knowledge about host and pathogen interactions helps the breeders and pathologists to understand their immune responses and pathological activities (Thangamalar *et al*., 2010).

Functions of humoral and cellular reactions in silkworm *Bombyx mori* L. Wan *et al.,* 2013 reported the presence of five different types of blood cells in silkworm haemolymph namely prohaemocytes, plasmatocytes, oenocytoids, granular and spherule cells and these cells produces various cellular reactions which initiates the process like phagocytosis, nodule formation and encapsulation of the foreign material causing engulfing and eating up of the pathogen. In addition to this silkworm humoral immune system functions with the activation of several proteins and more importantly with that of cascade proteins which triggers the release of several pigments responsible for melanization and coagulation cascade further activating the signaling system indicating the invasion of pathogen into the host body (Shao *et al.,* 2012).

The AMP genes in silkworm become functional by interference of disease causing microbes in the gut fluid or fat body tissues of the worm which results in the release of several peptides into the silkworm body fluid (Hoffmann and Reichhart 2002). Once these highly activated peptides gets accumulated in silkworm haemolymph, cause death of the foreign pathogen (Ferrandon *et al*., 2007). In addition to humoral and cellular, innate immunity is also the most important defense response provided by nature to the silkworm. Cellular immunity is the immunity provided by the hemocytes and is regarded as cellular immunity. Various types of hemocytes are present in silkworm namely, Prohemocytes (PRS), Plasmatocytes (PLS), Granulocytes (GRS), Spherulocytes (SLS), Oenocytoids (OE), Adipohaemocyte (AD) (Sun *et al.,* 2016).

In silkworm *Bombyx mori* L. six different classes of antimicrobial proteins (AMPs) have been recognized namely, cecropin, attacin, lebocin, moricin, gloverin and defensin containing approximately 40 amino acids effective against both gram positive and gram negative bacteria (Cheng *et al.,* 2006; Hong *et al.,* 2008; Sugiyama *et al.,* 1995; Furukawa *et al.,* 1997; Kawaoka *et al.,* 2008; Kaneko *et al.,* 2008; Wen *et al.,* 2009; Christensen *et al.,* 1988).

Li *et al.* (2014) performed an experiment with exposure of nanoparticles of titanium dioxide (TiO_2 NPs) on the action of 20E in *Bombyx mori*. The results revealed shortening of the molting duration by 8 hr and prolonged the molting peak period by 10 per cent. Solexa sequencing depicted a clear profile of the changes in gene expression in the brain of mature larvae in response to TiO_2NPS exposure for 72 hours posing considerable effects on hormonal action and metabolic regulation of the treated silkworms. The transcriptional levels of *pi3k* and *P70S6K*, which are involved in the target of the rapamycin (TOR) signaling pathway, were recorded to be accelerated from normal and thirty one genes were recorded to behave differentially in the treated larvae.

Functions of signal pathway in silkworm *Bombyx mori* L. Extensive studies on gemone analysis of drosophila and silkworm lead to the establishment of the fact that there are three important pathways involved in immune responses in drosophila and silkworm namely, Immunodeficiency signaling pathway (IMD) and Toll signaling pathways (Fig. 1) and Janus kinase/ signal transducer and activator of transcription (JAK/ STAT) signaling pathway (Geng *et al.,* 2016). IMD and Toll signaling pathways (Fig. 1)are believed to play role as signal induction pathways responsible for activation of AMP genes in silkworm (Pinheiro and Ellar 2006; Ferrandon *et al.,* 2007; Lemaitre and Hoffmann 2007; Aggarwal and Silverman 2008; Valanne *et al.,* 2011).

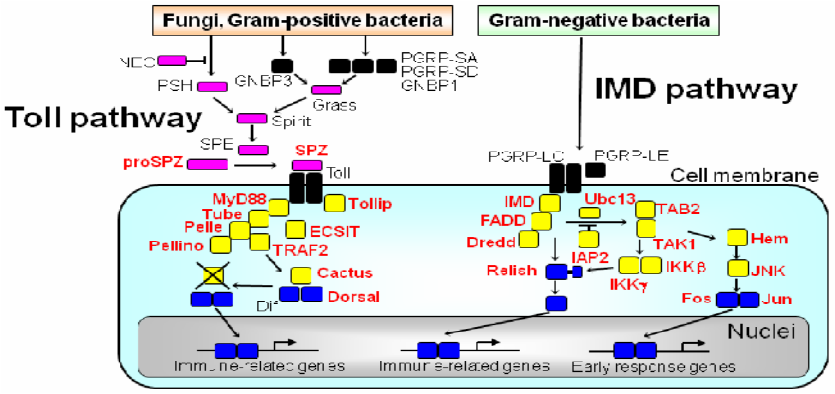

Fig. 1. IMD and Toll signaling pathways in silkworm *Bombyx mori* L. (Tanaka *et al.,* 2011).

IMD signaling pathway. The Immune deficiency or IMD pathway is considered as the primary mechanism used for recognisation, identification and elimination of disease causing pathogens particularly the bacterial spores in silkworm immune system. IMD signaling pathway functions actively and more efficiently for recognisation of gram positive strains of bacterial spp. and provides strong immunity in silkworm strains against bacterial diseases. IMD pathway in silkworm is triggered by certain meso-diaminopimelic acid containing peptidoglycan (PGN) (DAP-PGN) for defense against both gram positive and gram negative bacteria like *Bacillus* spp. (Gottar *et al.,* 2002; Ramet *et al*., 2002; Takehana *et al.,* 2002; Kaneko *et al.,* 2005).

Toll signaling pathway. Functioning of Toll pathway is governed by action of several polypeptides and in contrast with IMD pathway which offers defense particularly against bacterial spores, Toll pathway offers resistance against fungal infection (Hoffmann, 2003). Action of Toll pathway is stimulated by lysine containing PGN (Lys-PGN) after forming complex structure of PGN recognisation proteins including peptidoglycan recognisation protein- SA (PGRP-SA) and PGRP- SD and GNBP-1 and this complex activates Toll signaling pathway for recognisation and elimination of foreign material (Govert *et al.,* 2003; Pili-Floury *et al.,* 2004; Bischoff *et al.,* 2004).

Janus Kinase (JAK)/Signal Transducer and Activator of Transcription (STAT) or JAK/STAT signaling pathways. JAK/STAT signaling pathways plays very important role in providing defense against invading pathogens and play very significant role in processes including immune-regulation of various cytokines, cell proliferation, differentiation and more importantly in programmed cell death *i.e*. apoptosis (Brivanlou and Darnell 2002). JAK/ STAT signaling pathways has been extensively studied in Drosophila (Harrison *et al.,* 1998), and various signaling factors have been reported to play significant role in activation and functioning of JAK/STAT pathway. Such include, extracellular ligand, trans-membrane receptor, transcription factors, suppression of cytokine signaling family etc. (Arbouzova and Zeidler 2006). In *Bombyx mori* L. recent attempts have been made to understand the functioning of JAK/STAT signaling pathway which revealed similarities with that of Drosophila to a large extent but much work needed to be done regarding the mechanism of activation of the pathway (Li *et al.,* 2003, Rawlings *et al*., 2004 and Cheng *et al.,* 2009).

Participation of C-type lectins has been recognized in the functioning of JAK/STAT signaling pathway in case of silkworm *Bombyx mori* L. for recognisation of disease causing agents (Zhang *et al.,* 2014a, b). C-type lectins plays important role in recognisation of pathogen and over all cellular reaction (Vazquezmendoza *et al.,* 2013; Garcia-Vallejo and Kooyk 2015). JAK/STAT signaling pathway is reported to be relatively more active against *Beauveria bassiana* causing muscardine disease in silkworm (Hou *et al.,* 2013), however the exact correlation between is still under investigation as only a very little research has been conducted on this aspect (Liu *et al.,* 2013). Liang Jiang (2021) reported JAK/STAT signaling pathway to exhibit antiviral defense mechanism for imparting antiviral immunity in silkworm *Bombyx mori* (Table 1).

Induction of immunity in silkworm: Immunity in silkworm can also be induced artificially to some extent (Table 2) by the following experiments as reported by Nataraju *et al.* (2005).

Table 1: Defense responses in silkworm described by Nataraju *et al.* (2005).

Genes	Present in	Action
Bactericidal , bacteriostatic, fungicidal and other factors	Hemolymph	Bacteria , NPV , microsporidian *Nosema bombycis*
A red fluorescent protein	Silkworm midgut	Antiviral, agglutinating and inactivating viruses such as BmCPV and Bm NPV
Viral inhibitory factor	Hemolymph	Antiviral
Granulocytes	Hemolymph	Phagocytosis and prevention of NP, Prevents the growth of germ tube of *Beauveria bassiana*
Free medium chain fatty acids	Cuticle	Resistant to Aspergillosis
Peritropic membrane	Cuticle	Resistant to bacterial penetration and virus adsorption to the midgut epithelium
Epithelial cells of midgut		Prevents the adsorption of BmIFV, BmDNV and BmCPV
Integument	Skin	Anti-fungal action

Table 2: Artificial Induction of immunity in silkworm.

Agents	Treatment	Result
BmCPV	85ºC Temp. for 15 min.	30-50 % Inhibition of disease development
Anti-BmNPV serum and attenuated BmNPV	Triple vaccination	80-81 % Suppression of NP development
Interferons inducers *i.e*. Poly –IC and 2.5 A	Pre-oral inoculation	Suppress cytoplasmic polyhydrosis
Poly –IC and 2.5 Oligo (A)	Pre-oral inoculation	Suppress cytoplasmic polyhydrosis

CONCLUSION

Bombyx mori L. is an important economic insect used commercially for silk production and more recently used in molecular studies as a well recognized model organism. However, different categories of pathogens cause serious economic loss to sericulture industry by infecting silkworm larvae and depleting the chances of successful crop every year. Although silkworm *Bombyx mori* L. lacks a well developed acquired immune system but possesses a sophisticated innate immune system offering defense to the host against disease causing organisms. The innate immune responses of silkworm constitute both cellular and humoral reactions including the synthesis and release of antimicrobial peptides, phenoloxidase, phagocytosis, nodule formation, encapsulation and melanization. Innate immune responses are activated via means of IMD and Toll pathways which activate the secretion of AMPs and enable the host to control the gene expression in response to the invasion of foreign pathogens. Therefore, considering the economic and biomedical significance of silkworm an attempt has been carried out in this review to understand the complexity of silkworm immune system with a future prospective to breed disease resistant silkworm strains with high levels of immune responses. This could serve as an informative piece of literature for silkworm breeders with an objective to produce improved silkworm strains for strengthening sericulture industry in a big way.

Conflicts of Interest. None.

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How to cite this article: Suraksha Chanotra, Muzafar Ahmad Bhat, Jyoty Angotra, Gurvinder Raj Verma and Abdul Aziz (2022). Studies of Immune Responses in Silkworm *Bombyx mori* L.: A Review. *Biological Forum – An International Journal, 14*(4): 348-352.