FACULTY OF SCIENCE
UNIVERSITY OF SOUTH BOHEMIA
ČESKÉ BUDĚJOVICE

Ph.D. Thesis

Functional analysis of the bZIP transcription factor dATF3 in *Drosophila* development

Petra Sekyrová

Supervisor: Doc. RNDr. Marek Jindra, CSc.

Biology Centre of the Academy of Science of the Czech Republic,
Institute of Entomology, České Budějovice

České Budějovice 2009

Sekyrová P, 2009. Functional analysis of the bZIP transcription factor dATF3 in *Drosophila* development.
PhD Thesis, in English, 121 p. Faculty of Science, University of South Bohemia, České Budějovice, Czech Republic.

ANNOTATION

This thesis is based on reverse-genetic functional analyses of the bZIP transcription factor dATF3 in the *Drosophila* model. Genetic, molecular and microscopic techniques have been employed to reveal the first evidence for a developmental role of dATF3 in vivo and for its cooperation with its predicted partner, the bZIP protein dJun. The data show that dATF3 is essential for normal function of the fat body and hence for larval life. During metamorphosis, dATF3 expression is transcriptionally down-regulated to allow morphogenesis of the adult abdomen and of the compound eye. Deregulation of dATF3 at that time increases adhesiveness of larval epidermal cells in the abdomen, and thus blocks their extrusion and replacement with the adult epidermis. Besides its partner dJun, dATF3 interacts genetically with the ecdysone steroid signaling and with the Rho pathway. The results provide new information on dATF3 role in cell adhesion during epithelial morphogenesis and thus improve our understanding of basic developmental mechanisms.

FINANCIAL SUPPORT

My work was supported by research grants 2B06129 and 600766580 from the Czech Ministry of Education to Marek Jindra and by the Institute of Entomology research project Z50070508 from the Czech Academy of Sciences. I was also supported by a student grant 25/2005/P-BF from the Grant Agency of the University of South Bohemia.

DECLARATION

I hereby declare that I did all the work, presented in this thesis, by myself or in collaboration with the co-authors of the published article.

Further, I declare that in accordance with the Czech legal code § 47b law No. 111/1998 in its valid version, I consent to the publication of my Ph.D. thesis (in an edition made by removing marked parts archived by the Faculty of Science) in an electronic way in the public access to the STAG database run by the University of South Bohemia in České Budějovice on its web pages.

České Budějovice, 11 Ocotber, 2009 Petra Sekyrová

ACKNOWLEDGMENTS

I would like to thank my supervisor, Doc. RNDr. Marek Jindra, CSc., for scientific guidance and for introducing me to fly genetics. I appreciate his invaluable help with writing the manuscript and this thesis. I thank Prof. Dirk Bohmann for the opportunity to work in his laboratory. I am grateful to Mirka Uhlířová for her help during my stay in Prof. Bohmann's laboratory, both at the professional and personal levels. I would like to thank all members of Marek and Masako Jindra labs for friendly atmosphere and helpful discussions. My special thanks go to my family for overall support during my studies.

CONTENTS

RESEARCH OBJECTIVES

The family of basic region-leucine zipper (bZIP) transcription factors includes important regulators of stress-induced transcriptional response, many of which have predicted or proven roles in human diseases. As most of the published studies rely on ex-vivo cell culture systems, developmental roles of these proteins in vivo are comparatively less well-understood. The *Drosophila* model has been instrumental in defining in vivo functions of several bZIP proteins, such as the homologs of Jun and Fos, primarily in epithelial cell shape changes during morphogenesis and wound healing.

The Activating transcription factor 3 (ATF3) has thus far been studied only in mammalian systems, and numerous studies in cultured cell lines have implicated it in multiple cellular behaviors including stress response, cell proliferation, apoptosis, or cell motility. ATF3 has been shown to dimerize with other bZIP proteins, namely members of the Jun subfamily. Recent data from ATF3 knock-out mice or mice and rats with up-regulated ATF3 expression connect ATF3 with stress, inflammation, immune and metabolic homeostasis, and with injury and regeneration in vivo. Whether any of these processes involve a functional interaction between ATF3 and its partner Jun is not known. Also, since the ATF3-deficient mice are viable, it is unclear whether, besides its obvious physiological importance, ATF3 plays any role in animal development.

The goal of my study was to explore a potential developmental role of the ATF3 ortholog in the fruit fly *Drosophila melanogaster*, and thus improve our understanding of its function in general. A special emphasis was on the predicted, but not proven, in vivo interaction between ATF3 and Jun. We chose the *Drosophila* model for the variety of superb genetic tools it offers to study protein functions and interactions in the context of the intact organism. The aims of the work were to document the biochemical interaction between *Drosophila* ATF3 (dATF3) and its putative partner dJun, and to find out whether this interaction had any biological relevance. Using both loss-of-function and gain-of-function approaches in live animals, we aimed to determine which developmental processes required dATF3 or were affected by it, respectively. Based on the obtained phenotypic changes, we planned genetic interaction studies that would reveal functional relationships between dATF3 and signaling pathways acting in particular developmental events.

LIST OF ABBREVIATIONS

20E - 20-hydroxyecdysone

AJ - Adherens Junctions

AP - After Pupariation

AP-1 – Activator Protein 1

APF - After Puparium Formation

ATF - Activating transcription factor

Awh - Arrowhead

BMP - Bone Morphogenetic Protein

BR-C - Broad complex

Bsk - basket

bZIP – basic region-leucine Zipper

CA - Constitutively Active

Cdc42 - Cell division control protein 42

Cnc - Cap'n'collar

Crc - Cryptocephal

Creb - cAMP response element binding

CycG - Cyclin G

DIAP - Drosophila Inhibitor of Apoptosis

Dm myb - *Drosophila melanogaster* myb

DN - Dominant Negative

Dpp - Decapentaplegic

DRICE - Drosophila Ice.

DRONC - Drosophila Nedd2-like caspase

EcR - Ecdysone Receptor

eIF2α - eukaryotic Initiation Factor 2

ER – Endoplasmic Reticulum

Esg - Escargot

Flp - Flippase

Flw - Flapwing

gadd153 – Growth arrest and DNA-damage-inducible protein GADD153

GFP - Green Fluorescent Protein

Gt - Giant

Hep - Hemipterous

Hid - Head involution defective

JH - Juvenile Hormone

JNK - Jun N-terminal Kinase

Kr-h1 - Krüppel homolog 1

LE - Leading Edge

LEC – Larval Epidermal Cell

LPS - Lipopolysaccharide

LRF-1 - Liver Regenerating Factor 1

MHC – Myosin Heavy Chain

MLCP - Myosin II Light Chain Phosphatase

MRLC - non-muscle Myosin II Regulatory Light Chain

NF-ELAM1 - nuclear Factor-Endothelial Leukocyte Adhesion Molecule 1

Pdp1 - PAR-domain protein 1

Puc - Puckered

PVF1 - Platelet Vascular Factor 1

RNAi – RNA interference

Rok - Rho kinase

Rpr - Reaper

SAPK - Stress-Activated Protein Kinase

SERCA ATPase - Sarco/Endoplasmic Reticulum Ca^{2+} ATPase

Sis-A - Sisterless A

Slbo - Slow border cells

Slpr - Slipper

Sqh – Spaghetti Squash

StRE – Stress Response Element

TDF - Tracheae Defective

TGF-β - Transforming Growth Factor β

TNF-α - Tumor Necrosis Factor α

UAS - Upstream Activating Sequence

UPR – Unfolded Protein Response

Usp- Ultraspiracle

VEGF/PDGF - Vascular Endothelial Growth Factor/Platelet Derived Growth factor

Vri - Vrille

Zip - Zipper

INTRODUCTION

1. Epithelial remodeling during *Drosophila* development requires JNK signaling

During *Drosophila* development dramatic epithelial remodeling occurs. From a larva that lacks any external appendages a complex adult fly emerges with a head, legs, wings and other structures. Adult epithelia originate from imaginal cells, either imaginal discs or histoblasts, all of which become specified already during embryogenesis of the fly. Imaginal discs are compact structures of folded epithelia. Each imaginal disc contains spatially distinct pre-patterned areas which will fully differentiate and extend during metamorphosis, at the pupal stage. Imaginal discs give rise to excorporate structures including the head, antennae, thorax, wings and halteres, legs, and external genitals. Incorporate structures such as the gut, salivary glands or abdominal epidermis possess islets or rings of imaginal cells, also termed histoblasts, embedded within the original larval tissue. The imaginal histoblasts are diploid cells, arrested before transition to the S phase, that do not divide during larval stages (Ninov et al., 2009; Jiang and Edgar, 2009; Hayashi and Yamaguchi, 1999). At the onset of metamorphosis histoblasts rapidly proliferate and replace polyploid larval cells that had formed the organs so far. Therefore, adult epithelia originating from histoblasts are made by gradual replacement of larval cells with the newly proliferating and differentiating adult cells, while those adult structures that develop from imaginal discs rather arise by coordinated movements of entire epithelial sheets.

Multiple signaling pathways control these complex processes at different levels. Hormonal signaling controls the overall synchronicity of developmental events in distinct organs. Patterning of the body plan is regulated by cascades of homeotic genes. Signaling within individual cells responds to these general impulses.

In *Drosophila*, Jun N-terminal kinase (JNK) signaling (Fig. 1) has been known to play a role in most cases of epithelial remodeling during development. Embryonic dorsal closure (Glise et al., 1995; Riesgo-Escovar et al., 1996, Hou et al., 1997, Kockel et al., 1997, Riesgo-Escovar and

Hafen 1997a and 1997b, Zeitlinger et al., 1997; Glise and Nosseli, 1997; Martín-Blanco et al., 1998, Stronach and Perrimon, 2002) and adult thorax closure (Zeitlinger and Bohmann, 1999; Martín-Blanco et al., 2000) are well-studied examples. JNK pathway was also shown to affect development of the compound eye (Bohmann et al., 1994) and the external terminalia (Polaski et al., 2006; Macías et al., 2004), as well as oogenesis (Suzanne et al., 2001; Dobens et al., 2001) and wound healing (Rämet et al., 2002; Bosch et al., 2005).

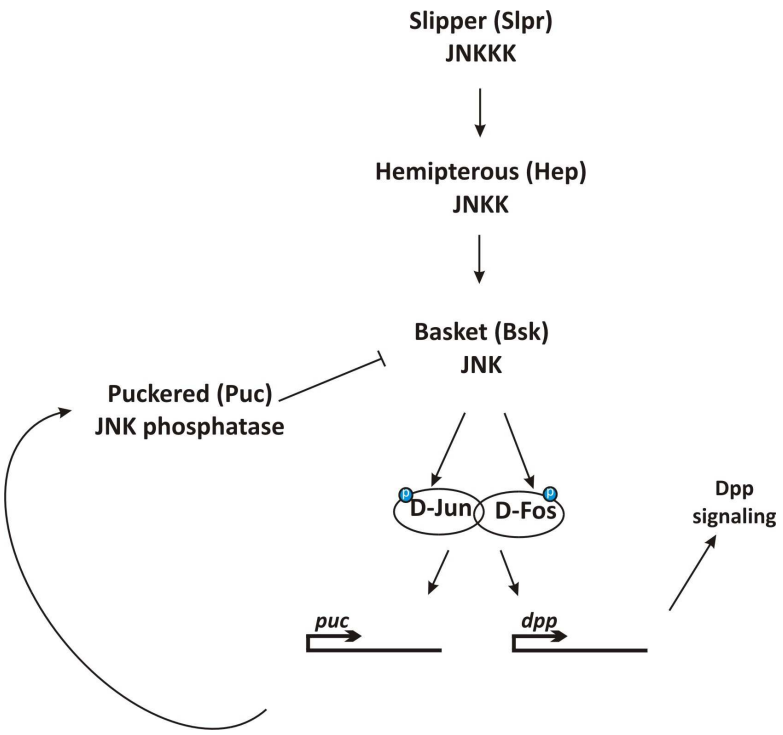

Fig 1. **JNK signaling pathway in *Drosophila*.** A cascade of kinases leads to phosphorylation of the bZIP transcription factors dJun and dFos which dimerize and trigger transcription of *puckered* (*puc*) and *decapentaplegic* (*dpp*) among other target genes. *puckered* encodes a JNK phosphatase and accomplishes a negative feedback regulation of the signaling pathway. Dpp, *Drosophila* Transforming growth factor β/Bone Morphogenetic Protein (TGF-β/BMP) ortholog, regulates cell shape and polarity changes during morphogenesis. The molecular composition of the JNK pathway is well-conserved between *Drosophila* and mammals except that in flies each of its components is usually encoded by single gene, thus minimizing potential functional redundancy (Kockel et al., 2001).

1.1. Embryonic dorsal closure

During embryonic dorsal closure, lateral sheets of elongating epidermal cells advance to close the dorsal part of the embryo that is occupied by the amnioserosa. Amnioserosa cells concomitantly extrude from the epithelial plane by apical constriction and drop into the interior of the embryo where they are eliminated by apoptosis (Fig. 2) (Kiehart et al., 2000; Toyama et al., 2008). Epithelial cells do not proliferate during dorsal closure and the movement of epithelial sheets is a consequence of cell shape changes of epidermal cells which elongate in dorso-ventral axis. On both sides of the epidermal sheets the dorsal-most row of cells has a special function during the closure and it is termed the leading edge (LE). Cells in the LE contain an actomyosin-rich cable forming a “purse string”, which tightens the circle around the dorsal gap. LE cells from opposite sides approach and contact each other by extending thin actin-based filopodia and lamellipodia and eventually LE cells seal the gap as a zipper. Actin and non-muscle myosin II are necessary to generate active moving forces in leading edge, for apical contraction of amnioserosa and for proper zipping (Franke et al., 2005). Epidermal cells lateral to LE elongate and provide the main force which pushes the epithelial sheets towards dorsal midline.

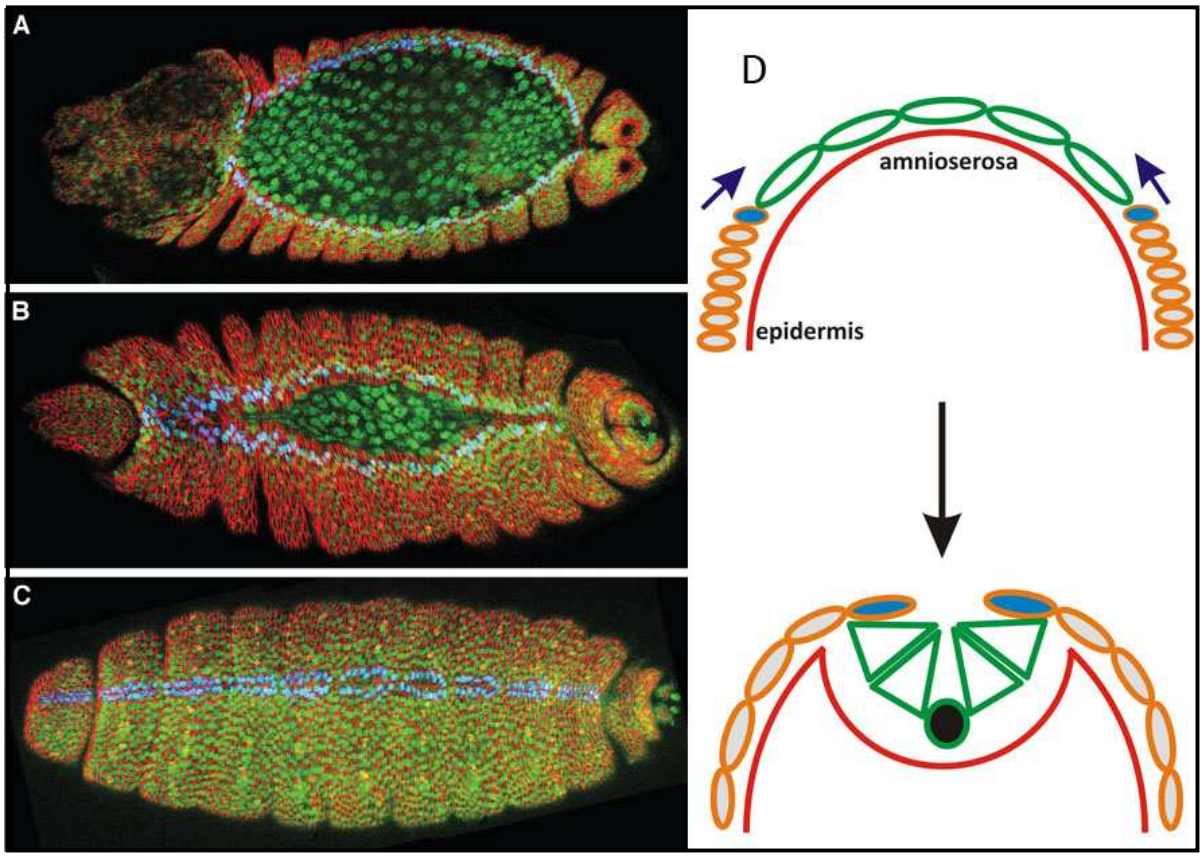

Figure 2. **Dorsal closure in the developing embryo.** (A)-(C) Dorsal views of whole *Drosophila* embryos. Leading edge cells with active JNK signaling are highlited by *puckered* expression (blue). Cell membranes are stained with anti-coracle antibody (red) and nuclei are marked with anti-dJun (green). Note large nuclei of amnioserosa cells in dorsal opening. (A) Stage 13 embryo, dorsal closure started. (B) Stage 14 embryo. (C) Stage 16 embryo, epidermal sheets from both sides have met each other at the dorsal midline and are closing the epithelial layer in a zipping manner. Adapted from (Kockel et al., 2001). (D) A schematic cross-section of developing embryo, dorsal side. Epidermal cells (orange) from both sides are elongating in dorso-ventral axis and bring two epithelial sheets to dorsal midline. Cells in leading edge express *puckered* (blue). Amnioserosa cells (green) are apically constricting and delaminating (black). Amnioserosa and epidermis remain continuous during the whole process and keep contact with the basal lamina (red). Adapted and modified from (Martín-Blanco et al., 2000).

During embryonic dorsal closure JNK signaling coordinates morphogenetic processes in cells of leading edge, lateral epidermis and amnioserosa. JNK pathway is active in a row of LE cells (shown by *puckered* expression in Fig. 2) and promotes cytoskeleton remodeling in LE as well as movement of lateral sheets. *Drosophila* mutants in components of the JNK signaling pathway die

as embryos due to severe dorsal closure defects (Glise et al., 1995; Riesgo-Escovar et al., 1996; Hou et al., 1997; Kockel et al., 1997; Riesgo-Escovar and Hafen, 1997a and 1997b; Martín-Blanco et al., 1998; Stronach and Perrimon 2002). Modulation of activity of the small GTPases Rho1, Cdc42 or Rac1 both by upregulation or downregulation leads in defects in dorsal closure as well (Strutt et al., 1997; Harden et al., 1999; Jacinto et al., 2000). Numerous studies performed on *Drosophila* embryos during dorsal closure implicate reciprocal crosstalk betveen JNK, Dpp (TGF-β/BMP ortholog, target of JNK signaling) and small GTPases signaling in all three segments of epidermal cells: leading edge, cells lateral to leading edge and amnioserosa (Riesgo-Escovar and Hafen, 1997b; Sluss and Davis, 1997; Glise and Nosseli, 1997; Zeitlinger et al., 1997; Harden et al., 1999; Ricos et al., 1999; Harden et al., 2002; Bloor and Kiehart, 2002; Conder et al., 2004; Fernández et al., 2007; Zahedi et al., 2008).

1.2. Thorax closure.

During metamorphosis imaginal discs grow, evert and finally diferentiate into adult structures. Wing/thorax discs are present in a pair giving rise to the left and right wings and left and right halves of the dorsal thorax, the notum (Fig. 3A-D). During adult thorax closure, imaginal cells have to crawl over the larval cells and proceed towards the dorsal midline, where they will fuse with their partners from the opposite wing/thorax disc. Larval cells eventually delaminate from the edges of the larval epidermal sheet and undergo apoptosis in the body cavity (Fig. 3E). Imaginal cells at the leading border emit filopodia to localize their counterparts on the opposite leading margin. Together with thickened filopodia, actin-rich bridges develop between the contralateral sheets. In contrast to embryonic dorsal closure, thoracic filopodia, besides their recognizing function, are believed to generate an active force that brings the two imaginal sheets towards the dorsal midline. Thus, there is no purse-string mechanism involved in thorax closure.

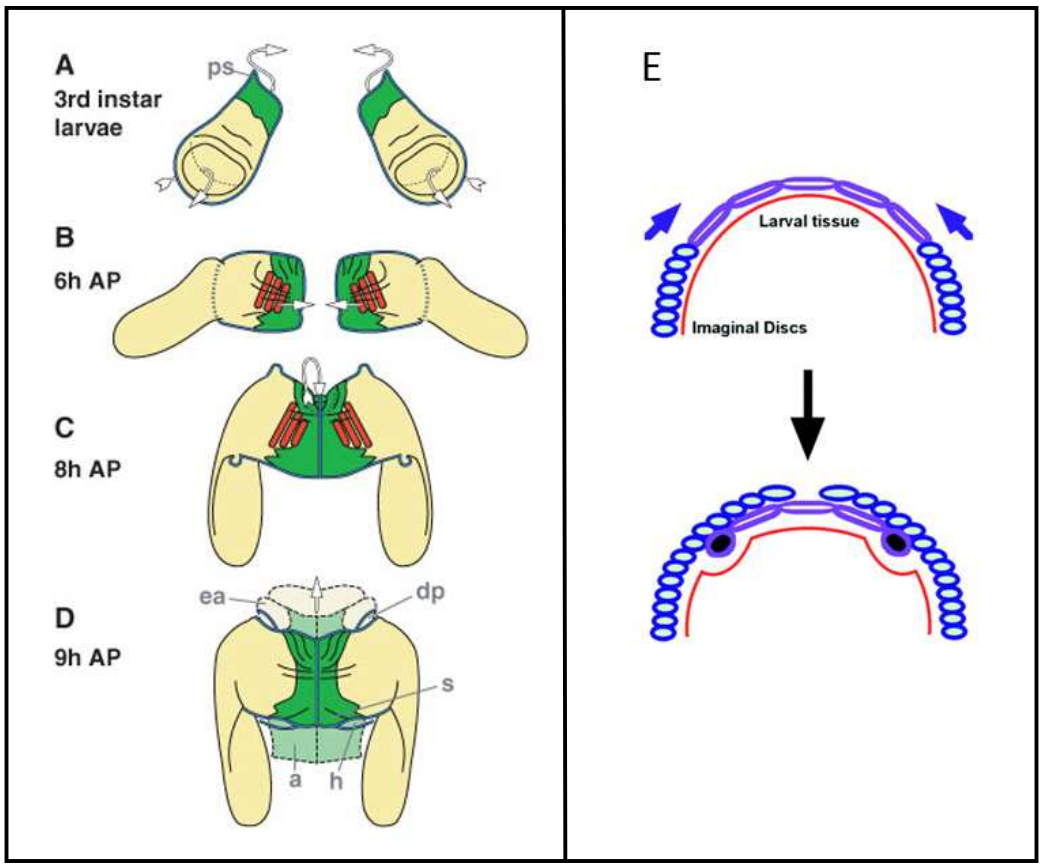

Figure 3. **Adult thorax closure during metamorphosis.** (A)–(D) Schematic representation of imaginal discs which give rise to wing (yellow parts) and thorax (green). (A) The imaginal discs will evert after pupariation (arrows). (B)–(D) After pupariation (AP), everted adult epithelial structures approach to each other and enclose the adult thorax. Adapted from (Kockel et al., 2001). (E) A cross-section of the dorsal part of the developing thorax. Imaginal cells (blue) detach from the basal lamina (red) and crawl over the larval cells (purple). Larval cells then delaminate from the borders of the larval epidermal sheet and undergo apoptosis (black). Adapted from (Martín-Blanco et al., 2000).

As in dorsal closure, JNK signaling is activated in the leading row of imaginal cells closing the thorax as documented by *puckered* expression (Zeitlinger and Bohmann 1999; Martín-Blanco et al., 2000). Impaired JNK signaling (loss of dFos, dJun, Hemipterous, slipper or overexpression of *puckered*) results in defects of thoracic epithelial fusion at the dorsal midline, manifest as a cleft (Zeitlinger and Bohmann 1999; Jindra et al., 2004; Polaski et al., 2006; Martín-Blanco et al., 2000). PVR, a receptor of PVF1 (Platelet Vascular Factor 1), a *Drosophila* relative of the

mammalian VEGF/PDGF (Vascular Endothelial Growth Factor/Platelet Derived Growth factor) growth factors, has been shown to activate JNK signaling during thorax closure. *PVR* mutants have cleft thorax, however, they do not show defects in embryonic dorsal closure (Ishimaru et al., 2004).

1.3. Formation of adult terminalia

In the adult fly, terminalia are comprised by internal and external genitalia, analia and the hindgut. The terminalia arise from a single genital imaginal disc. During pupal metamorphosis the shaping process involves fusion of the left and right halves of the imaginal disc, disc eversion, and in males a 360° clockwise rotation that is associated with maturation of the internal genitalia (Ádám et al., 2003; Sánchez and Guerrero 2001). The exact mechanism of epithelial remodeling and joining of the adult terminal structures to the epithelia of the abdominal segments remains unclear.

JNK signaling and apoptosis are involved in terminalia differentiation. Altering these pathways leads to defects in terminalia rotation and eversion. In addition, this is often accompanied with abdominal clefts or segment fusions. *slpr* (JNKKK) mutation or $slpr^{DN}$ expression lead to sterile females with truncated terminal structures and to males with malrotated or missing terminalia. *hep* (JNKK) hypomorphic females also show truncation or deletion of terminalia (Polaski et al., 2006). Suppression of JNK signaling by overexpression of *puc* (JNK phosphatase) in the genital disc causes defects in rotation of male terminalia. Abolishing of PVF1/PVR/JNK signaling by PVF1 mutation or $PVF1^{DN}$ also causes malrotated male terminalia (Macías et al., 2004).

Blocking apoptosis at various signaling levels results in abdominal defects. Overexpression of the baculovirus caspase inhibitor p35, mutations in *head involution defective* (*hid*), one of the *Drosophila* apoptotic activators, or mutations in the *Drosophila* effector caspase *Ice* all lead to abdominal cleft and malrotated male terminalia (Abbott and Lengyel 1991; Macías et al., 2004; Muro et al., 2006; this work).

1.4. Morphogenesis of the adult abdominal epidermis

1.4.1. Adult abdominal epidermis is made from histoblasts

Abdominal histoblasts are established in the embryo as four pairs of nests for each abdominal segment. Anterior dorsal nest (approximately 16 cells) and posterior dorsal nest (aproximately 5 cells) give rise to the tergite. Ventral nest (approx. 16 cells) produces the sternite and pleurite, and the spiracular nest (approx. 3 cells) forms the spiracle (Fig. 4) (Madhavan and Madhavan 1980; Ninov et al. 2007).

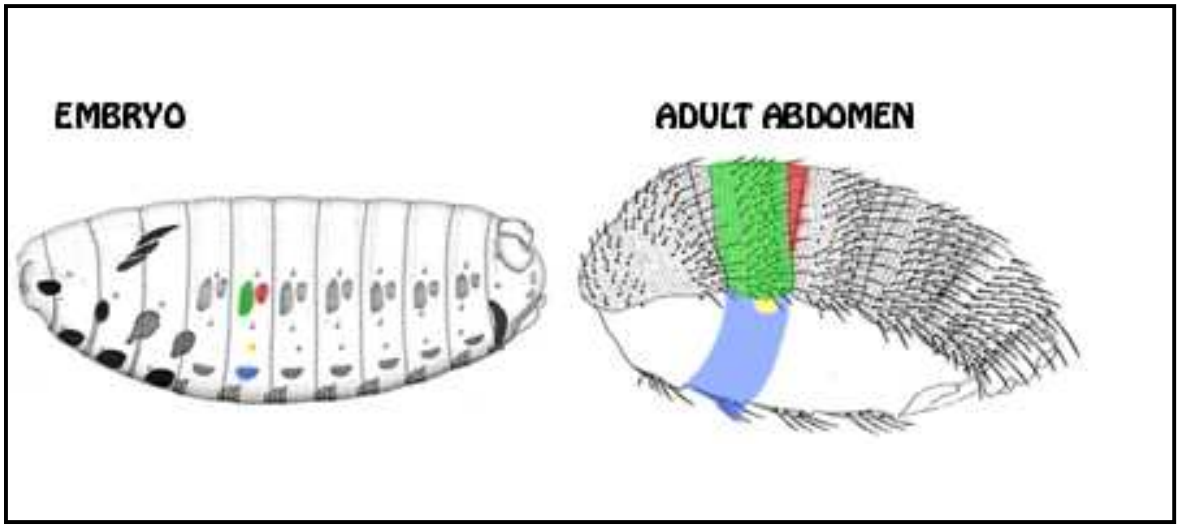

Figure 4. **Embryonal histoblasts are precursors of the adult epidermis.** Histoblasts are set up as four nests on each side of every abdominal segment. During metamorphosis each nest gives rise to the corresponding part of the adult epithelium. Green: dorsal anterior nest. Red: dorsal posterior nest. Blue: Ventral nest. Yellow: spiracular nest. Adapted from (Ninov et al., 2007).

During the entire larval development histoblasts do not increase in number and start to divide only after the onset of metamorphosis, which is marked by puparium formation (or pupariation). They proliferate in two waves. Upon pupariation histoblasts divide rapidly and without growth; the G1 phase is reduced to minimum. From 15 to 36 hours after puparium formation (APF) G1 phases prolong to several hours allowing the new histoblasts to grow. At 15 h APF histoblasts start to migrate from original nests and replace larval epidermal cells (LECs), which

continuously delaminate from the epithelial sheet and die. From 24 to 36 h APF histoblasts spread from lateral sides and fuse with adjacent nests (within segments and also intersegmentally) to cover most of the abdomen, first ventrally and laterally. Finally the expanding sheets of histoblasts meet at the dorsal midline and close the adult epidermis. The integrity of the single-layered epidermal sheet has to remain intact during the replacement process and delamination of LECs must be synchronized and coordinated with the proliferation and spreading of histoblasts (Fig. 5).

Obr. 5 obsahuje utajované skutečnosti a je obsažen pouze v archivovaném originále disertační práce uloženém na Přírodovědecké fakultě

Figure 5. **Exchange of the abdominal epidermal cells during metamorphosis.** (A) Dorsal abdominal epidermis of wild-type pupa 24 hours after puparium formation (APF). Histoblasts (h, small diploid cells) spread from lateral nests (arrows) and expand towards the dorsal midline (green rectangle). Larval epidermal cells (LECs, large polyploid cells) will gradually delaminate and die. Magenta: nuclei stained with DAPI, green: α-Catenin::GFP fusion protein marks cell membranes. (B) A schematic cross-section of the dorsal abdomen. Histoblasts (green) proliferate and expand from nests while LECs (blue) extrude from the epithelial plane, undergo apoptosis and are engulfed by macrophages in the body cavity. The process continues from lateral sides towards the dorsal midline.

At 36 - 40 hours APF the abdomen is completely covered with adult epidermis exclusively consisting of histoblast cells which start to differentiate and deposit adult cuticle. By 72 h APF the trichomes and bristles are formed and by 90 hours APF the cuticle of the pharate adult becomes sclerotized and pigmented. Adult abdominal epidermis is thus made in two phases: first, LECs are replaced with histoblasts and second, histoblasts differentiate into adult epidermal or neuronal cells and produce sclerotized and hairy adult cuticle (Fig. 6).

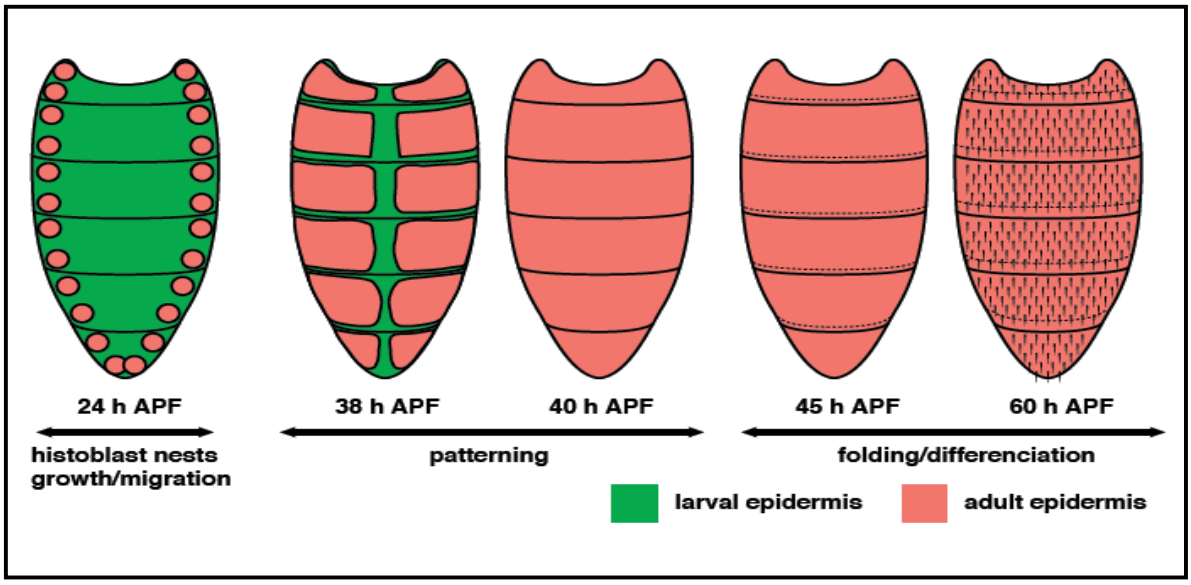

Figure 6. **Two populations of epidermal cells exchange during abdominal metamorphosis.** Larval cells (green) are succeeded by histoblasts (pink) which after defining their position start to differentiate and produce adult trichomes and bristles. Dorsal view, adapted from (N. Gompel, methods used in laboratory: http://www.ibdml.univ-mrs.fr/equipes/BP_NG). The timing of the events may be somewhat delayed compared to Ninov et al. (2007) or our observations.

1.4.2. Ecdysone signaling in the abdominal remodeling

Metamorphosis of the *Drosophila* larva to pupa and adult is controlled by the steroid hormone ecdysone and its active form 20-hydroxyecdysone (20E), respectively. A pulse of ecdysone titer at the late L3 stage initiates the metamorphic program. Massive death of larval organs is accompanied by development of adult tissues (Fig. 7).

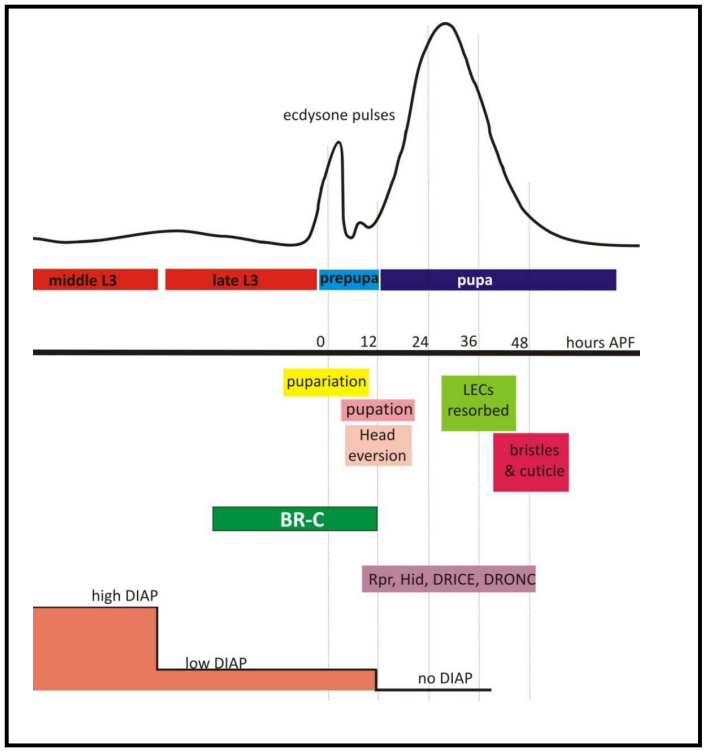

Figure 7. **Ecdysone pulses regulate metamorphosis.** Ecdysone peak at late L3 larval stage triggers puparium formation (pupariation). Another ecdysone pulse around 10-12 hours after puparium formation (APF) activates adult head eversion (pupation). 36 hours APF most LECs are substituted with histoblasts which synthesize adult cuticle and form sensory bristles. *Broad complex* (***BR-C***) gene activates transcription of apoptotic executors: Reaper **(Rpr)** and head involution defective (**Hid)** (which will subsequently sequester the crucial caspase inhibitor protein, **DIAP** - *Drosophila* Inhibitor of Apoptosis), an initiator caspase **DRONC** (*Drosophila* Nedd2-like caspase) and effector caspase **DRICE** (*Drosophila* Ice). Adapted and modified from (Emery et al., 2004; Thummel, 1996; Thummel, 2001; Kornbluth and White, 2005; Yin and Thummel, 2004; Yin et al., 2007).

Tissues sense ecdysone through a heterodimeric nuclear receptor Usp/EcR. *Drosophila* EcR proteins are found in three different splicing variants, each with specific roles depending on place and time where it is expressed. EcR-A, EcR-B1 and EcR-B2 share common DNA- and ligand-binding domains and differ in their N-terminal sequences. EcR-A is mainly expressed in imaginal discs while EcR-B1 predominates in larval tissues and in histoblasts (Talbot et al., 1993). After puparium formation EcR-A and EcR-B1 are coexpressed in both histoblasts and LECs (Ninov et al., 2007). *EcR-B1* and *EcR-A* mutations or EcR^{RNAi}-mediated inhibition of ecdysone sensing in histoblasts abolishes their proliferation, while EcR^{DN} version expressed in LECs inhibits their apical constriction and consequent apoptosis. Thus, ecdysone receptor signaling is necessary in both histoblasts and LECs (Bender et al., 1997, Davis et al., 2005; Ninov et al., 2007), although the role of the 20E ligand has not been demonstrated.

Broad-Complex (*BR-C*) is among the earliest *Drosophila* genes activated in response to the ecdysone pulse. At the onset of metamorphosis distinct BR-C protein isoforms trigger transcription of specific sets of genes which in turn execute the metamorphosis program involving making of pupal structures as well as destruction of larval tissues. *BR-C* encodes four protein isoforms (Z1-Z4), each of which has a unique combination of zinc finger domains and is expressed in tissue-specific manner. Distinct isoforms promote expression of pupal-specific genes but have to be down-regulated later in adult development (Zhou and Riddiford, 2002; Minakuchi et al. 2008; Emery et al. 1994). Artificial overall induction of BR-C Z1 at 44-48 h APF causes re-expression of pupal cuticle genes and suppression of adult cuticle genes. Depending on time of BR-C induction the animals have impaired pigmentation and bristle formation in abdominal segments although the epidermis consists entirely of histoblasts (Zhou and Riddiford, 2002, Minakuchi et al., 2008). A similar phenotype is observed after artificial treatment with Juvenile Hormone (JH) during the larval-pupal transition. JH normally acts against ecdysone signaling by preventing metamorphic development. In *Drosophila* this effect of JH is limited to the abdomen, where ectopic JH causes prolonged expression of *BR-C* (Zhou and Riddiford, 2002) and, consistently with the effect of BR-C Z1 misexpression itself, prevents the adult program. This results in pharate adults lacking adult cuticle and bristles on the abdomen. Misexpression of another JH-induced gene, *Krüppel homolog 1* (*Kr-h1*), specifically in histoblasts has a similar effect – it prevents the decline of BR-C expression and differentiation of

the adult cuticle, producing animals with a stripe of bald pupal cuticle at the dorsal abdominal midline (Minakuchi et al., 2008).

1.4.3. Mechanism of LEC extrusion

Delamination of LECs from the epithelial sheet is promoted by apical constriction of the actomyosin complex. The contraction depends on phosphorylation of non-muscle myosin II regulatory light chain (MRLC), in *Drosophila* encoded by *spaghetti squash* (*sqh*). This phosphorylation will activate non-muscle myosin II heavy chain, which is encoded by *zipper* (*zip*). Permanent dephosphorylation of Sqh in LECs by myosin light chain phosphatase (MLCP) inhibits the myosin contractility, resulting in LECs occupying the epidermal sheet at postmetamorphosis periods. By contrast, constitutive phosphorylation of Sqh by Rho kinase (Rok) increased the rate of LEC delamination. (Ninov et al., 2007). Rok is activated by Rho1 small GTPase (also known as RhoA). GTP-bound active form of Rho1 promotes conformational change of Rok, which is then able to phosphorylate its target Sqh. A direct link between Rho1 signaling and myosin II activity is genetically evidenced also from other tissues (developing embryo, leg and wing) (Halsell et al. 2000). Through proper organization of actin and myosin II in epidermis, Rho1 is required to form adherens junctions (AJ) during *Drosophila* embryogenesis. Rho1 establishes apicolateral distribution of spectrin and targets *Drosophila* E-cadherin to AJ. Moreover, Rho1 physically interacts with catenins α and p120 (Magie et al., 2002; Bloor and Kiehart, 2002). Rho1 RNAi causes abdominal cleft (this work).

Genetic interactions between non-muscle myosin and the JNK pathway have been demonstrated in the *Drosophila* wing disc (Fig. 8). A phosphatase Flapwing (Flw) dephosphorylates Sqh subunit, thereby deactivating Zip, which in turn results in inhibition of *puc* expression. Constitutively active hep^{CA} enhances Flw deficiency in *flw* mutants, which is then suppressed in *bsk* mutants (Kirchner et al., 2007).

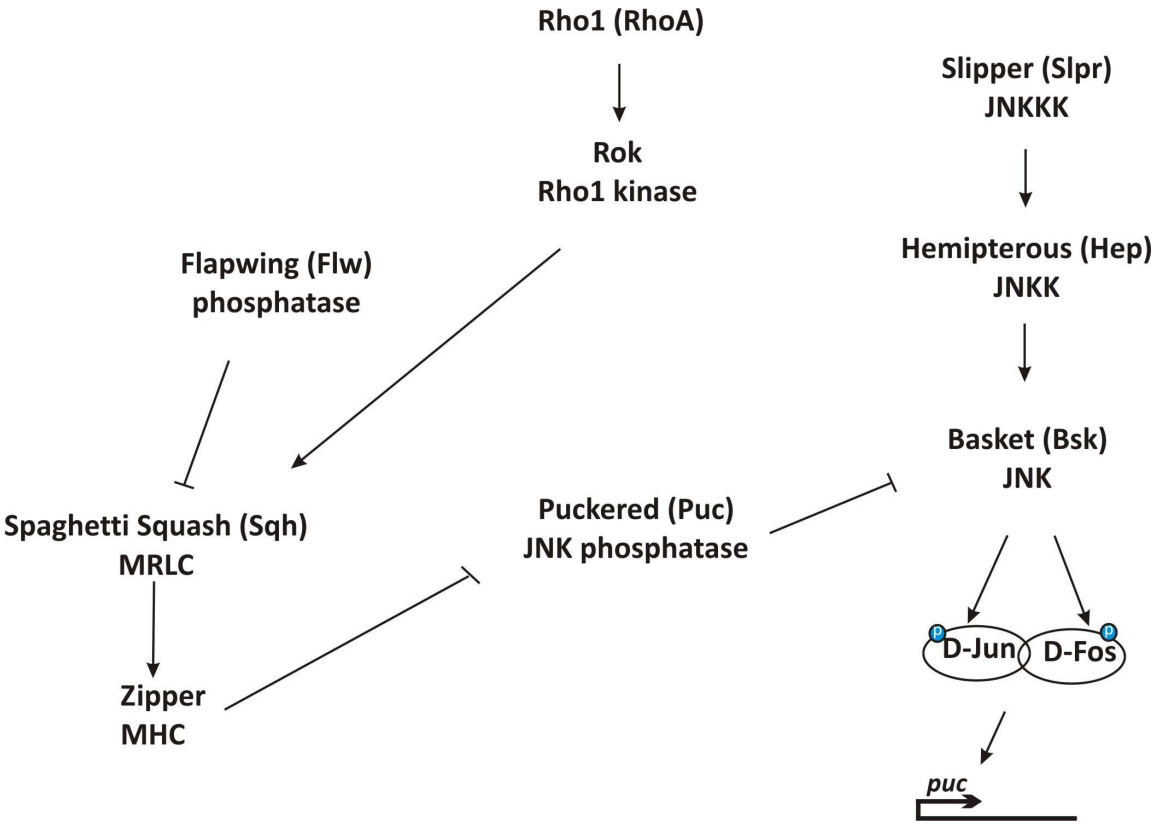

Fig. 8. **Interaction between JNK and Rho1 signaling** as revealed by genetic experiments in *Drosophila* wing imaginal disc (Kirchner et al., 2007).

1.4.4. Genes affecting histoblast proliferation

In addition to EcR, which is required for the initial phase of synchronized histoblast divisions early after the onset of metamorphosis (Ninov et al., 2009), there are other genetic factors whose loss disrupts abdominal morphogenesis by affecting histoblast proliferation or fate decision. This can occur at several stages of development for different reasons:

1. Insufficient numbers of histoblasts specified during embryogenesis

***Arrowhead* (*Awh*)** mutants have fewer than normal cells in the abdominal histoblast nests in embryos and larvae. Thus, although differentiation of histoblasts after pupariation is normal,

pharate adults have completely "naked" abdomen that lacks adult cuticle and bristles. Awh is a transcription factor that ensures production and survival of abdominal histoblasts and salivary gland ring imaginal cells. Interestingly, Awh is not necessary to establish imaginal discs as *Arrowhead* mutations have no impact on their development (Curtiss and Heilig, 1995).

2. Insufficient proliferation of histoblasts during pupal development

Ubiquitous RNAi silencing of **cyclin G (CycG)** perturbes proliferation and fusion of dorsal histoblast nests after puparium formation. However, loss of CycG does not affect histoblast numbers in embryos or larvae and does not alter their ploidy (Salvaing et al., 2008). During adult metamorphosis, ***Dm myb*** mutants do not have enough histoblasts to replace all larval cells, suggesting a defect in cell proliferation. The rate of histoblast proliferation in *Dm myb* mutants after puparium formation is slower and cells are stuck at pre-metaphase or pre-prophase. In the course of development percentage of histoblasts with mitotic abnormalities increases and adults display a stripe of bald cuticle at the dorsal abdominal midline (Fung et al., 2002).

3. Polyploid histoblasts

Unlike cells within *Drosophila* larval tissues that are highly polyploid, the dividing imaginal cells including abdominal histoblast are diploid. ***escargot*** (***esg***) mutants die as pharate adults with thin and transparent abdominal cuticle at the dorsal midline. LECs remain in the abdominal epithelium. *esg* mutant larvae have polyploid histoblasts with reduced expression of Cyclin A, a marker of the G2/M cell cycle stage, which is normally abundant in larval abdominal histoblasts (Hayashi et al. 1993). Similarly ***Cdc2*** mutants have polyploid histoblasts in larvae (Hayashi 1996). Thus, although in both *esg* and *cdc2* mutants the initial numbers of histoblasts in embryos and larvae are normal, the histoblasts proliferate more slowly than wild-type after puparium formation because of their higher ploidy.

4. Unknown mechanism

Cryptocephal **(*crc*)** encodes several isoforms homologous to the mammalian bZIP transcription factor ATF4. Several mutant alleles display undifferentiated abdomen. The molecular mechanism has not been suggested (Hewes et al., 2000).

2. ATF3, a bZIP protein

Activating transcription factors (ATFs) were so named in 1987 to refer to proteins that bind the adenovirus early promoters E2, E3 and E4 at sites with a common core sequence CGTCA (Lee et al., 1987). ATF3 was originally detected as a liver regenerating factor 1 (LRF-1) due to its presence in rat liver after partial hepatetomy (Hsu et al., 1991). The majority of known data about transcription factor ATF3 concerns the human protein and mainly comes from studies performed in cultured cell lines. Animal models like rats or mice overexpressing human ATF3, and *Atf3*$^{-/-}$ knock-out mice were also developed. Due to a vast number of studies on mammalian ATF3, I will mention here only a small subset of published data that are relevant to our work.

2.1. Leucine zippers

ATF3 belongs to the basic region-leucine zipper (bZIP) family and the ATF subfamily of transcription factors. The ATF subfamily contains several members divided into 6 subgroups. Proteins within each subgroup share significant similarity both inside and outside the bZIP domain. Proteins between the subgroups, however, do not share much similarity other than the bZIP motif itself (Hai and Hartman, 2001).

Members of the bZIP family form selective heterodimers through their bZIP domains and recognize DNA consensus elements (Fig. 9). The heterodimers have different binding activity than their respective homodimers. Heterodimers of ATF3 with c-Jun and JunB activate transcription, while ATF3/c-Fos formation has not been observed (Lee et al., 1987; Hsu et al., 1991, 1992). Fos proteins form heterodimers with Jun-related proteins, but do not homodimerize, whereas c-Jun forms dimers with all Jun- and Fos- related proteins. ATF3 also binds ATF2 but not ATF1 (Hai and Curran, 1991). Another binding partner for ATF3 is the ER stress-activated bZIP protein gadd153 (Chen et al., 1996; Wolfgang et al., 1997). Distinct bZIP dimers act as transcriptional activators or repressors and bind to DNA response elements. Human ATF3 homodimer binds to DNA within the ATF/CRE consensus site (TGACGTCA) and potentially several other sites such as AP-1, ELAM-1, E4F, StRE (Liang et al., 1996; Gong et al., 2002).

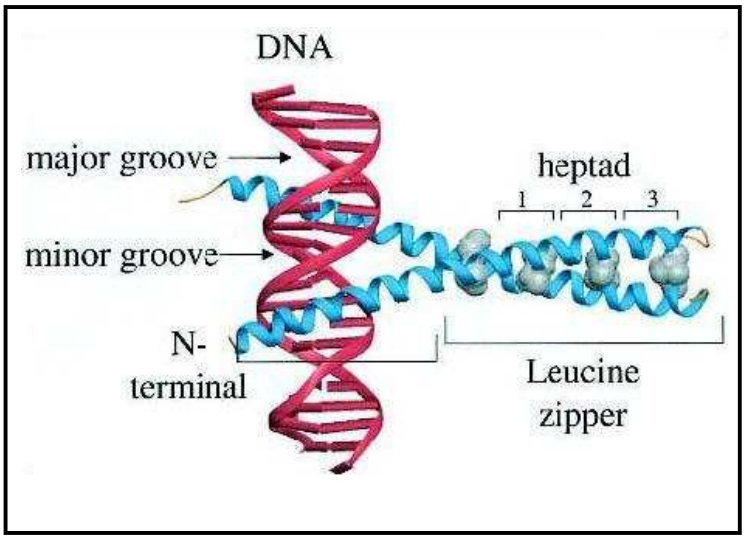

Figure 9. **Model of bZIP dimer binding to DNA.** Several heptads of characteristic amino acid sequence (including leucines at specific positions) form the leucine zipper dimerization domain. The basic domains bind to the major groove in the DNA helix. Adapted from (Ellenberger et al., 1992).

In the *Drosophila* genome, 27 genes coding for known or putative bZIP proteins have been identified, and 21 of them have mammalian counterparts (Rubin et al., 2000, Fassler et al., 2002). Several *Drosophila* bZIP proteins were studied genetically: dFos and dJun proteins (Perkins et al., 1998, 1990), a PAR-domain protein 1 (Pdp1) (Zhang et al., 1990), cap'n'collar (cnc) (Mohler et al., 1991), giant (gt) (Capovilla et al., 1992), slow border cells (slbo) (Roth and Montell, 1992), crebA (Smolik et al., 1992), creB-17A (Usui et al., 1993), sisterless A (sis-A) (Erickson and Cline, 1993), vrille (vri) (George and Terracol, 1997), Tracheae Defective (TDF) (Eulenberg and Schuh, 1997), and cryptocephal (crc), an ATF4 homologue (Hewes et al., 2000). Strikingly, a *Drosophila* gene encoding a homolog of ATF3 (referred to as *A3-3* or *CG11405* in the FlyBase) has not yet been functionally characterized, and is the subject of this work.

2.2. ATF3 modulates the response to stress in cooperation with JNK signaling

Mammalian ATF3 is an adaptive early-response gene whose product appears in the cell within first hours of the reaction to stress. Under normal conditions most cells have low or undetectable levels of ATF3 mRNA, but it is rapidly upregulated upon various stress stimuli. Together with its binding partner, which is often c-Jun, ATF3 binds to promoters of various target genes and affects the cellular response. Depending on the type of stress, ATF3 may promote antagonistic responses such as apoptosis or proliferation.

ATF3 expression together with c-jun and JNK activation, is induced under **oxidative and genotoxic stress** and usually targets cell to apoptotic death. An interplay between ATF3 and p53 in the context of oxidative stress has also been suggested (Yin et al., 1997; Shtil et al., 1999; Allen-Jenings, 2001; Nobori et al., 2002; Abe et al., 2003; Kang et al., 2003; Andley et al., 2004; Mallory et al., 2005; Koike et al., 2005; Yoshida et al., 2008; Turchi et al., 2008). The proapoptotic action of ATF3 has been demonstrated in several types of cancer cells where ATF3 activity induced caspases (Mashima et al., 2001; Syed et al., 2005). Recent study shows that it depends on stage of tumor progression and its metastatic potential whether ATF3 will cause apoptosis or uncontrolled proliferation (Yin et al., 2008).

ATF3 expression significantly increases during **inflammation**. Several studies show that ATF3 promotes cell proliferation upon serum addition. ATF3 restored the delayed progression of G1 phase. It induced the expression of cyclins D1, A and E and activated cell-cycle kinases CDK2 and CDK4 (Allan et al., 2001, Tamura et al., 2005). Upon TNF-α treatment ATF3 protected cells from TNFα-dependent apoptosis (Kawauchi et al., 2002). TNF-α induces ATF3 via JNK, while ERK signaling antagonizes TNFα-mediated ATF3 expression (Inoue et al., 2004, Nawa et al., 2002). ATF3 is rapidly induced after exposure to TNF-α and in the form of heterodimer with c-jun it can suppress E-selectin gene transcription, possibly via binding to NF-ELAM1 site, previously occupied by an activating ATF2/c-jun complex (Cai et al., 2000). ATF3 is induced by nitric oxide in endothelial cells (Chen and Wang, 2004) and it is also induced in liver by lipopolysaccharide (LPS) (Hartman et al., 2004). ATF3 is significantly upregulated and translocated to the cell nucleus in mouse lung treated with ovalbumin, causing asthma-like inflammation (Gilchrist et al., 2008).

ATF3 is activated also during **ER stress**. Homocystein, a reducing agent, causes rapid induction of ATF3 expression that together with JNK signaling triggers the apoptotic death. Tunicamycin, a glycosylation inhibitor, activates the JNK/SAPK signaling and ATF3 expression. During ER stress initiated by thapsigargin treatment, which inhibits SERCA ATPase (sarco/endoplasmic reticulum Ca^{2+}), thus depleting ER calcium stores, ATF3 elevation is caused by phosphorylated eIF2α (Cai, 2000; Zhang, 2001;. Jiang et al.; 2004, Tamura et al.; 2005).

Injury caused by partial removal of an organ or a nerve transection causes immediate elevation of ATF3 mRNA. ATF3 is even widely used as a specific and sensitive neuronal marker of axonal injury where it regulates **regeneration** in heterodimer with c-jun (Hsu et al., 1991; Chen et al., 1996; Allen-Jenings et al., 2001; Gold et al., 1993; Tsujino et al., 2000; Tsuzuki et al., 2001; Obata et al., 2003; Pearson et al., 2003; Ohba et al., 2004; Taylor et al., 2005; Isacsson et al., 2005; Peters et al., 2005; Stewart, 1995; Soares et al., 2001; Hunt et al., 2004; Lindwall and Kanje, 2005; Seijffers et al., 2007; Kiryu-Seo et al. 2008).

ATF3 knock-out mice as well as ATF3 overexpressing mice and rats are viable but suffer from disturbed glucose homeostasis. Moreover, ATF3 overexpressing animals show multiple organ dysfunctions in the liver, pancreas and heart (Allen-Jenings, 2001; Okamoto et al., 2001; Hartman et al., 2004).

Mammalian ATF3 is extensively studied and has been reported to play a role in all kinds of stress and important processes such as inflammation, tumorigenesis, proliferation and apoptosis. The results are often contradictory and seem not to give coherent answer on ATF3 function. Thus, reverse genetics may be the possible way how to elucidate the importance of ATF3 occurrence in the cell. We have used the excellent *Drosophila* model which offers many genetic and molecular tools to uncover some of the ATF3 roles, primarily during animal development.

RESULTS

Petra Sekyrova, Dirk Bohmann, Marek Jindra, Mirka Uhlirova. **Interaction between *Drosophila* bZIP proteins dATF3 and dJun prevents replacement of epithelial cells during metamorphosis.**

Accepted in Development

Petra Sekyrova has done 80% of the work

Epithelial sheet spreading and fusion underlie important developmental processes. Well-characterized examples of such epithelial morphogenetic events have been provided by studies in *Drosophila*, and include embryonic dorsal closure, formation of the adult thorax, and wound healing. All of these processes require the basic region-leucine zipper (bZIP) transcription factors dJun and dFos. Much less is known about morphogenesis of the fly abdomen, which involves replacement of larval epidermal cells (LECs) with adult histoblasts that divide, migrate and finally fuse to form the adult epidermis during metamorphosis. Here, we implicate *Drosophila* Activating transcription factor 3 (dATF3), the single ortholog of human ATF3 and JDP2 bZIP proteins, in abdominal morphogenesis. During the process of the epithelial cell replacement, transcription of the *datf3* gene declines. When this down-regulation is experimentally prevented, the affected LECs accumulate cell-adhesion proteins and their extrusion and replacement with histoblasts are blocked. The abnormally adhering LECs consequently obstruct the closure of the adult abdominal epithelium. This closure defect can be either mimicked and further enhanced by knockdown of the small GTPase RhoA or, conversely, alleviated by stimulating the ecdysone steroid hormone signaling. Both Rho and ecdysone pathways have been previously identified as effectors of the LEC replacement. To elicit the gain-of-function effect, dATF3 specifically requires its binding partner dJun. Our data thus identify dATF3 as a new functional partner of *Drosophila* Jun during development.

Růst a spojování epiteliálních vrstev jsou součástí důležitých vývojových dějů. Dobře prostudované příkady těchto morfologických změn, např. proces uzavírání embrya (dorsal closure), vývoj thoraxu u dospělce nebo hojení ran, pochází ze studia mouchy *Drosophily*. Žádný ze zmíněných procesů se neobejde bez bZIP (basic region-leucine zipper) faktorů dJun a dFos. O vývoji dospělčího abdomenu není známo téměř nic. Zde probíhá výměna larválních epidermálních buněk (LECs) za dospělčí histoblasty, které se během metamorfózy dělí, migrují a následně spojují, aby daly vznik epidermální vrstvě pokrývající abdomen dospělce. V předkládané publikaci poukazujeme na roli dATF3, jediného ortologu lidských proteinů ATF3 a JDP2, v morfogenezi abdomenu *Drosophily*. V průběhu výměny epidermálních buněk klesá úroveň transkripce genu *datf3*. Pokud je tento pokles experimentálně zablokován, postižené LEC buňky akumulují proteiny buněčných spojů a nejsou schopny delaminovat z epidermální vrstvy a tudíž nejsou nahrazeny histoblasty. LEC buňky s abnormální adhezivitou pak blokují uzavření abdominálního epitelu. Podobného efektu je dosaženo také snížením exprese RhoA, malé GTPázy nebo naopak, defekt je zahojen stimulací ekdysonové dráhy. Dřívější studie ukazují, že se obě dráhy, Rho a ekdysonová dráha, účastní výměny epidermálních LEC buněk. K vyvolání fenotypu potřebuje dATF3 specificky protein dJun. Naše data ukazují, že dATF3 je nový funkční partner proteinu Jun v průběhu vývoje mouchy *Drosophila*.

UNPUBLISHED RESULTS

Tato část práce (strana 77-100) obsahuje utajované skutečnosti a je obsažena pouze v archivovaném originále disertační práce uloženém na Přírodovědecké fakultě

METHODS

Tato část práce (strana 101 - 114) obsahuje utajované skutečnosti a je obsažena pouze v archivovaném originále disertační práce uloženém na Přírodovědecké fakultě

REFERENCES

Abbott MK, Lengyel JA. (1991) Embryonic head involution and rotation of male terminalia require the Drosophila locus head involution defective. Genetics. 129(3):783-9.

Abe T, Oue N, Yasui W, Ryoji M. (2003) Rapid and preferential induction of ATF3 transcription in response to low doses of UVA light. Biochem Biophys Res Commun. 310(4): 1168-74.

Adám G, Perrimon N, Noselli S. (2003) The retinoic-like juvenile hormone controls the looping of left-right asymmetric organs in Drosophila. Development. 130(11):2397-406.

Allan CA, Pestell RG, LaMarre J. (2001) Activating Transcription Factor 3 Induces DNA Synthesis and Expression of Cyclin D1 in Hepatocytes J. Biol. Chem. 276: 27272 - 27280.

Allen-Jennings AE, Hartman MG, Kociba GJ, Hai T. (2001) The Roles of ATF3 in Glucose Homeostasis. J Biol Chem. 276(31):29507-14.

Andley UP, Patel HC, Xi JH, Bai F. (2004) Identification of genes responsive to UV-A radiation in human lens epithelial cells using complementary DNA microarrays. Photochem Photobiol. 80:61-71.

Bayer CA, Halsell SR, Fristrom JW, Kiehart DP, von Kalm L. (2003) Genetic interactions between the RhoA and Stubble-stubbloid loci suggest a role for a type II transmembrane serine protease in intracellular signaling during Drosophila imaginal disc morphogenesis. Genetics. 165(3):1417-32.

Bender M, Imam FB, Talbot WS, Ganetzky B, Hogness DS. (1997) Drosophila ecdysone receptor mutations reveal functional differences among receptor isoforms. Cell. 91(6):777-88.

Bloor JW, Kiehart DP. (2002) Drosophila RhoA regulates the cytoskeleton and cell-cell adhesion in the developing epidermis. Development. 129(13):3173-83.

Bohmann D, Ellis MC, Staszewski LM, Mlodzik M. (1994) Drosophila Jun mediates Ras-dependent photoreceptor determination. Cell. 78(6):973-86.

Bosch M, Serras F, Martín-Blanco E, Baguñà J. (2005) JNK signaling pathway required for wound healing in regenerating Drosophila wing imaginal discs. Dev Biol. 280(1):73-86.

Brand AH, Perrimon N. (1993) Targeted gene expression as a means of altering cell fates and generating dominant phenotypes. Development. 118(2):401-15.

Bruey-Sedano N, Alabouvette J, Lestradet M, Hong L, Girard A, Gervasio E, Quennedey B, Charles JP. (2005) The Drosophila ACP65A cuticle gene: deletion scanning analysis of cis-regulatory sequences and regulation by DHR38. Genesis. 43(1):17-27.

Cai Y, Zhang C, Nawa T, Aso T, Tanaka M, Oshiro S, Ichijo H, Kitajima S. (2000) Homocysteine-responsive ATF3 gene expression in human vascular endothelial cells: activation of c-Jun NH(2)-terminal kinase and promoter response element. Blood. 96(6):2140-8.
Cakouros D, Daish T, Martin D, Baehrecke EH, Kumar S. (2002) Ecdysone-induced expression of the caspase DRONC during hormone-dependent programmed cell death in Drosophila is regulated by Broad-Complex. J Cell Biol. 157(6):985-95.
Cakouros D, Daish TJ, Kumar S. (2004) Ecdysone receptor directly binds the promoter of the Drosophila caspase dronc, regulating its expression in specific tissues. J Cell Biol. 165(5):631-40.
Capovilla M, Eldon ED, Pirrotta V. (1992) The giant gene of Drosophila encodes a b-ZIP DNA-binding protein that regulates the expression of other segmentation gap genes. Development. 114(1):99-112.
Chen BP, Wolfgang CD, Hai T. (1996) Analysis of ATF3, a transcription factor induced by physiological stresses and modulated by gadd153/Chop10. Mol Cell Biol. 16(3):1157-68.
Chen, H-H., Wang, DL. (2004) Nitric Oxide Inhibits Matrix Metalloproteinase-2 Expression via the Induction of Activating Transcription Factor 3 in Endothelial Cells Mol. Pharmacol. 65: 1130 - 1140.
Cherbas L, Hu X, Zhimulev I, Belyaeva E, Cherbas P. (2003) EcR isoforms in Drosophila: testing tissue-specific requirements by targeted blockade and rescue. Development. 130(2):271-84.
Chou TB, Perrimon N. (1992) Use of a yeast site-specific recombinase to produce female germline chimeras in Drosophila. Genetics. 131(3):643-53.
Chou TB, Noll E, Perrimon N. (1993) Autosomal P[ovoD1] dominant female-sterile insertions in Drosophila and their use in generating germ-line chimeras. Development. 119(4):1359-69.
Colombani J, Raisin S, Pantalacci S, Radimerski T, Montagne J, Léopold P. (2003) A nutrient sensor mechanism controls Drosophila growth. Cell. 114(6):739-49.
Conder R, Yu H, Ricos M, Hing H, Chia W, Lim L, Harden N. (2004) dPak is required for integrity of the leading edge cytoskeleton during Drosophila dorsal closure but does not signal through the JNK cascade. Dev Biol. 276(2):378-90.
Curtiss J, Heilig JS. (1995) Establishment of Drosophila imaginal precursor cells is controlled by the Arrowhead gene. Development. 121(11):3819-28.
Davis MB, Carney GE, Robertson AE, Bender M. (2005) Phenotypic analysis of EcR-A mutants suggests that EcR isoforms have unique functions during Drosophila development. Dev Biol. 282(2):385-96.
Dobens LL, Martín-Blanco E, Martínez-Arias A, Kafatos FC, Raftery LA. (2001) Drosophila puckered regulates Fos/Jun levels during follicle cell morphogenesis. Development. 128(10):1845-56.
Ellenberger TE, Brandl CJ, Struhl K, Harrison SC. (1992) The GCN4 basic region leucine zipper binds DNA as a dimer of uninterrupted alpha helices: crystal structure of the protein-DNA complex. Cell. 71(7): 1223-37.
Emery IF, Bedian V, Guild GM. (1994) Differential expression of Broad-Complex transcription factors may forecast tissue-specific developmental fates during Drosophila metamorphosis. Development. 120(11):3275-87.
Erickson JW, Cline TW. (1993) A bZIP protein, sisterless-a, collaborates with bHLH transcription factors early in Drosophila development to determine sex. Genes Dev. 7(9):1688-702.
Eulenberg KG, Schuh R. (1997) The tracheae defective gene encodes a bZIP protein that controls tracheal cell movement during Drosophila embryogenesis.EMBO J. 16(23):7156-65.
Fassler J, Landsman D, Acharya A, Moll JR, Bonovich M, Vinson C. (2002) B-ZIP proteins encoded by the Drosophila genome: evaluation of potential dimerization partners. Genome Res. 12(8):1190-200.
Fernández BG, Arias AM, Jacinto A. (2007) Dpp signalling orchestrates dorsal closure by regulating cell shape changes both in the amnioserosa and in the epidermis. Mech Dev. 124(11-12):884-97.
Fleming IN, Elliott CM, Exton JH. (1996) Differential translocation of rho family GTPases by lysophosphatidic acid, endothelin-1, and platelet-derived growth factor. J Biol Chem. 271(51):33067-73.
Franke JD, Montague RA, Kiehart DP. (2005) Nonmuscle myosin II generates forces that transmit tension and drive contraction in multiple tissues during dorsal closure. Curr Biol. 15(24):2208-21.
Fung SM, Ramsay G, Katzen AL. (2002) .Mutations in Drosophila myb lead to centrosome amplification and genomic instability. Development. 129(2):347-59.
George H, Terracol R. (1997)The vrille gene of Drosophila is a maternal enhancer of decapentaplegic and encodes a new member of the bZIP family of transcription factors. Genetics. 146(4):1345-63.
Gilchrist M, Henderson WR Jr, Clark AE, Simmons RM, Ye X, Smith KD, Aderem A. (2008) Activating transcription factor 3 is a negative regulator of allergic pulmonary inflammation. J Exp Med. 205(10):2349-57.
Glise B, Bourbon H, Noselli S. (1995) hemipterous encodes a novel Drosophila MAP kinase kinase, required for epithelial cell sheet movement. Cell. 183(3):451-61.

Glise B, Noselli S. (1997) Coupling of Jun amino-terminal kinase and Decapentaplegic signaling pathways in Drosophila morphogenesis. Genes Dev. 11(13):1738-47.
Gold BG, Storm-Dickerson T, Austin DR. (1993) Regulation of the transcription factor c-JUN by nerve growth factor in adult sensory neurons. Neurosci Lett. 154(1-2): 129-33.
Gong P, Stewart D, Hu B, Vinson C, Alam J. (2002) Multiple basic-leucine zipper proteins regulate induction of the mouse heme oxygenase-1 gene by arsenite. Arch Biochem Biophys. 405(2):265-74.
Gotwals PJ, Fristrom JW. (1991) Three neighboring genes interact with the Broad-Complex and the Stubble-stubbloid locus to affect imaginal disc morphogenesis in Drosophila. Genetics. 127(4):747-59.
Hai T, Curran T. (1991) Cross-family dimerization of transcription factors Fos/Jun and ATF/CREB alters DNA binding specificity. Proc Natl Acad Sci U S A. 88(9):3720-4.
Hai T, Hartman MG. (2001) The molecular biology and nomenclature of the activating transcription factor/cAMP responsive element binding family of transcription factors: activating transcription factor proteins and homeostasis. Gene. 273(1):1-11.
Halsell SR, Chu BI, Kiehart DP. (2000) Genetic analysis demonstrates a direct link between rho signaling and nonmuscle myosin function during Drosophila morphogenesis. Genetics. 155(3):1253-65.
Harden N, Ricos M, Ong YM, Chia W, Lim L. (1999) Participation of small GTPases in dorsal closure of the Drosophila embryo: distinct roles for Rho subfamily proteins in epithelial morphogenesis. J Cell Sci. 112 (Pt 3):273-84.
Harden N, Ricos M, Yee K, Sanny J, Langmann C, Yu H, Chia W, Lim L. (2002) Drac1 and Crumbs participate in amnioserosa morphogenesis during dorsal closure in Drosophila. J Cell Sci. 115(Pt 10):2119-29.
Hartman, MG, Lu D, Kim ML, Kociba GJ, Shukri T, Buteau J, Wang X, Frankel WL, Guttridge D, Prentki M, Grey ST, Ron D, Hai T. (2004) Role for activating transcription factor 3 in stress-induced beta-cell apoptosis. Mol Cell Biol. 24(13):5721-32.
Hayashi S, Hirose S, Metcalfe T, Shirras AD. (1993) Control of imaginal cell development by the escargot gene of Drosophila. Development. 118(1):105-15.
Hayashi S. (1996) A Cdc2 dependent checkpoint maintains diploidy in Drosophila. Development. 122(4):1051-8.
Hayashi S, Yamaguchi M. (1999) Kinase-independent activity of Cdc2/cyclin A prevents the S phase in the Drosophila cell cycle. Genes Cells. 4(2):111-22.
Hewes RS, Schaefer AM, Taghert PH. (2000) The cryptocephal gene (ATF4) encodes multiple basic-leucine zipper proteins controlling molting and metamorphosis in Drosophila. Genetics. 155(4):1711-23.
Hou XS, Goldstein ES, Perrimon N. (1997) Drosophila Jun relays the Jun amino-terminal kinase signal transduction pathway to the Decapentaplegic signal transduction pathway in regulating epithelial cell sheet movement. Genes Dev. 11(13):1728-37.
Hsu JC, Laz T, Mohn KL, Taub R. (1991) Identification of LRF-1, a leucine-zipper protein that is rapidly and highly induced in regenerating liver. Proc Natl Acad Sci U S A. ;88(9):3511-5.
Hsu JC, Bravo R, Taub R. (1992) Interactions among LRF-1, JunB, c-Jun, and c-Fos define a regulatory program in the G1 phase of liver regeneration. Mol Cell Biol. 12(10):4654-65.
Hunt D, Hossain-Ibrahim K, Mason MR, Coffin RS, Lieberman AR, Winterbottom J, Anderson PN. (2004) ATF3 upregulation in glia during Wallerian degeneration: differential expression in peripheral nerves and CNS white matter. BMC Neurosci. 2004 Mar 4;5:9.
Inoue, K., Zama, T., Kamimoto, T., Aoki, R., Ikeda, Y., Kimura, H., Hagiwara, M. (2004) TNFα-induced ATF3 expression is bidirectionally regulated by the JNK and ERK pathways in vascular endothelial cells. Genes to Cells. 9:59-70
Isacsson A, Kanje M, Dahlin LB. (2005) Induction of activating transcription factor 3 (ATF3) by peripheral nerve compression. Scand J Plast Reconstr Surg Hand Surg. 2005;39(2):65-72.
Ishimaru S, Ueda R, Hinohara Y, Ohtani M, Hanafusa H. (2004) PVR plays a critical role via JNK activation in thorax closure during Drosophila metamorphosis. EMBO J. 23(20):3984-94.
Jacinto A, Wood W, Balayo T, Turmaine M, Martinez-Arias A, Martin P. (2000) Dynamic actin-based epithelial adhesion and cell matching during Drosophila dorsal closure. Curr Biol. 10(22):1420-6.
Jiang C, Baehrecke EH, Thummel CS. (1997) Steroid regulated programmed cell death during Drosophila metamorphosis. Development. 124(22):4673-83.
Jiang C, Lamblin AF, Steller H, Thummel CS. (2000) A steroid-triggered transcriptional hierarchy controls salivary gland cell death during Drosophila metamorphosis. Mol Cell. 5(3):445-55.
Jiang HY, Wek SA, McGrath BC, Lu D, Hai T, Harding HP, Wang X, Ron D, Cavener DR, Wek RC. (2004) Activating transcription factor 3 is integral to the eukaryotic initiation factor 2 kinase stress response. Mol Cell Biol. 24(3):1365-77.

Jiang H, Edgar BA. (2009) EGFR signaling regulates the proliferation of Drosophila adult midgut progenitors. Development. 136(3):483-93.
Jindra M, Gaziova I, Uhlirova M, Okabe M, Hiromi Y, Hirose S. (2004) Coactivator MBF1 preserves the redox-dependent AP-1 activity during oxidative stress in Drosophila. EMBO J. 23(17):3538-47.
Kang Y, Chen CR, Massague J. (2003) A self-enabling TGFbeta response coupled to stress signaling: Smad engages stress response factor ATF3 for Id1 repression in epithelial cells. Mol Cell. 11(4):915-26.
Katz S, Heinrich R, Aronheim A. (2001) The AP-1 repressor, JDP2, is a bona fide substrate for the c-Jun N-terminal kinase. FEBS Lett. 506(3):196-200.
Katz S, Aronheim A. (2002) Differential targeting of the stress mitogen-activated protein kinases to the c-Jun dimerization protein 2. Biochem. J. 368:939-945
Kawauchi J, Zhang C, Nobori K, Hashimoto Y, Adachi MT, Noda A, Sunamori M, Kitajima S. (2002) Transcriptional repressor activating transcription factor 3 protects human umbilical vein endothelial cells from tumor necrosis factor-alpha-induced apoptosis through down-regulation of p53 transcription. J Biol Chem. 277(41):39025-34.
Kiehart DP, Galbraith CG, Edwards KA, Rickoll WL, Montague RA. (2000) Multiple forces contribute to cell sheet morphogenesis for dorsal closure in Drosophila. J Cell Biol. 149(2):471-90.
Kilpatrick ZE, Cakouros D, Kumar S. (2005) Ecdysone-mediated up-regulation of the effector caspase DRICE is required for hormone-dependent apoptosis in Drosophila cells. J Biol Chem. 280(12):11981-6.
Kirchner J, Gross S, Bennett D, Alphey L. (2007) The nonmuscle myosin phosphatase PP1beta (flapwing) negatively regulates Jun N-terminal kinase in wing imaginal discs of Drosophila. Genetics. 175(4):1741-9.
Kiryu-Seo S, Kato R, Ogawa T, Nakagomi S, Nagata K, Kiyama H. (2008) Neuronal injury-inducible gene is synergistically regulated by ATF3, c-Jun, and STAT3 through the interaction with Sp1 in damaged neurons. J Biol Chem. 283(11):6988-96.
Kockel L, Zeitlinger J, Staszewski LM, Mlodzik M, Bohmann D. (1997) Jun in Drosophila development: redundant and nonredundant functions and regulation by two MAPK signal transduction pathways. Genes Dev. 11(13):1748-58.
Kockel L, Homsy JG, Bohmann D. (2001) Drosophila AP-1: lessons from an invertebrate. Oncogene. 20(19):2347-64.
Koike M, Shiomi T, Koike A. (2005) Identification of Skin injury-related genes induced by ionizing radiation in human keratinocytes using cDNA microarray. J Radiat Res (Tokyo). 46(2):173-84.
Kornbluth S, White K. (2005) Apoptosis in Drosophila: neither fish nor fowl (nor man, nor worm) J. Cell Sci. 118: 1779 - 1787.
Lee KA, Hai TY, SivaRaman L, Thimmappaya B, Hurst HC, Jones NC, Green MR. (1987) A cellular protein, activating transcription factor, activates transcription of multiple E1A-inducible adenovirus early promoters. Proc Natl Acad Sci U S A. 84(23):8355-9.
Li T, Bender M. (2000) A conditional rescue system reveals essential functions for the ecdysone receptor (EcR) gene during molting and metamorphosis in Drosophila. Development. 127(13):2897-905.
Liang G, Wolfgang CD, Chen BP, Chen TH, Hai T. (1996) ATF3 gene. Genomic organization, promoter, and regulation. J Biol Chem. 271(3):1695-701.
Lindwall C, Kanje M. (2005) Retrograde axonal transport of JNK signaling molecules influence injury induced nuclear changes in p-c-Jun and ATF3 in adult rat sensory neurons.Mol Cell Neurosci. 29(2):269-82.
Macías A, Romero NM, Martín F, Suárez L, Rosa AL, Morata G. (2004) PVF1/PVR signaling and apoptosis promotes the rotation and dorsal closure of the Drosophila male terminalia. Int J Dev Biol. 48(10):1087-94.
Madhavan MM, Madhavan K. (1980) Morphogenesis of the epidermis of adult abdomen of Drosophila. J Embryol Exp Morphol. 60:1-31.
Magie CR, Pinto-Santini D, Parkhurst SM. (2002) Rho1 interacts with p120ctn and alpha-catenin, and regulates cadherin-based adherens junction components in Drosophila. Development. 129(16):3771-82.
Mallory JC, Crudden G, Oliva A, Saunders C, Stromberg A, Craven RJ. (2005) A novel group of genes regulate susceptibility to anti-neoplastic drugs in highly tumorigenic breast cancer cells. Mol Pharmacol. 68(6):1747-56.
Martín-Blanco E, Gampel A, Ring J, Virdee K, Kirov N, Tolkovsky AM, Martinez-Arias A. (1998) puckered encodes a phosphatase that mediates a feedback loop regulating JNK activity during dorsal closure in Drosophila. Genes Dev. 12(4):557-70.
Martín-Blanco E, Pastor-Pareja JC, Garcia-Bellido A. (2000) JNK and decapentaplegic signaling control adhesiveness and cytoskeleton dynamics during thorax closure in Drosophila. Proc Natl Acad Sci U S A. 97(14):7888-93.

Mashima T, Udagawa S, Tsuruo T. (2001) Involvement of transcriptional repressor ATF3 in acceleration of caspase protease activation during DNA damaging agent-induced apoptosis. J Cell Physiol.188(3):352-8.
Michaelson D, Silletti J, Murphy G, D'Eustachio P, Rush M, Philips MR. (2001) Differential localization of Rho GTPases in live cells: regulation by hypervariable regions and RhoGDI binding. J Cell Biol. 152(1):111-26.
Minakuchi C, Zhou X, Riddiford LM. (2008) Krüppel homolog 1 (Kr-h1) mediates juvenile hormone action during metamorphosis of Drosophila melanogaster. Mech Dev. 125(1-2):91-105.
Mohler J, Mahaffey JW, Deutsch E, Vani K. (1995) Control of Drosophila head segment identity by the bZIP homeotic gene cnc. Development. 121(1):237-47.
Muro I, Berry DL, Huh JR, Chen CH, Huang H, Yoo SJ, Guo M, Baehrecke EH, Hay BA. (2006) The Drosophila caspase Ice is important for many apoptotic cell deaths and for spermatid individualization, a nonapoptotic process. Development. 133(17):3305-15.
Nakade K, Pan J, Yoshiki A, Ugai H, Kimura M, Liu B, Li H, Obata Y, Iwama M, Itohara S. (2007). JDP2 suppresses adipocyte differentiation by regulating histone acetylation. *Cell Death Differ* 14: 1398-1405.
Nawa T, Nawa MT, Adachi MT, Uchimura I, Shimokawa R, Fujisawa K, Tanaka A, Numano F, Kitajima S. (2002) Expression of transcriptional repressor ATF3/LRF1 in human atherosclerosis: colocalization and possible involvement in cell death of vascular endothelial cells. Atherosclerosis. 161(2): 281-91.
Ninov N, Chiarelli DA, Martín-Blanco E. (2007) Extrinsic and intrinsic mechanisms directing epithelial cell sheet replacement during Drosophila metamorphosis. Development. 134(2):367-79.
Ninov N, Manjón C, Martín-Blanco E. (2009) Dynamic control of cell cycle and growth coupling by ecdysone, EGFR, and PI3K signaling in Drosophila histoblasts. PLoS Biol. 7(4):e1000079.
Nobori K, Ito H, Tamamori-Adachi M, Adachi S, Ono Y, Kawauchi J, Kitajima S, Marumo F, Isobe M. (2002) ATF3 inhibits doxorubicin-induced apoptosis in cardiac myocytes: a novel cardioprotective role of ATF3. J Mol Cell Cardiol. 34(10):1387-97.
Obata K, Yamanaka H, Fukuoka T, Yi D, Tokunaga A, Hashimoto N, Yoshikawa H, Noguchi K. (2003) Contribution of injured and uninjured dorsal root ganglion neurons to pain behavior and the changes in gene expression following chronic constriction injury of the sciatic nerve in rats. Pain. 101(1-2):65-77.
Ohba N, Kiryu-Seo S, Maeda M, Muraoka M, Ishii M, Kiyama H. (2004) Expression of damage-induced neuronal endopeptidase (DINE) mRNA in peri-infarct cortical and thalamic neurons following middle cerebral artery occlusion. J Neurochem. 91(4):956-64.
Okamoto Y, Chaves A, Chen J, Kelley R, Jones K, Weed HG, Gardner KL, Gangi L, Yamaguchi M, Klomkleaw W, Nakayama T, Hamlin RL, Carnes C, Altschuld R, Bauer J, Hai T. (2001) Transgenic mice with cardiac-specific expression of activating transcription factor 3, a stress-inducible gene, have conduction abnormalities and contractile dysfunction. Am J Pathol. 159(2):639-50.
Pearson AG, Gray CW, Pearson JF, Greenwood JM, During MJ, Dragunow M. (2003) ATF3 enhances c-Jun-mediated neurite sprouting. Brain Res Mol Brain Res. 120(1):38-45.
Perkins KK, Admon A, Patel N, Tjian R. (1990) The Drosophila Fos-related AP-1 protein is a developmentally regulated transcription factor. Genes Dev. 4(5):822-34.
Perkins KK, Dailey GM, Tjian R. (1998) Novel Jun- and Fos-related proteins in Drosophila are functionally homologous to enhancer factor AP-1. EMBO J. 7(13):4265-73.
Peters CM, Ghilardi JR, Keyser CP, Kubota K, Lindsay TH, Luger NM, Mach DB, Schwei MJ, Sevcik MA, Mantyh PW. (2005) Tumor-induced injury of primary afferent sensory nerve fibers in bone cancer pain. Exp Neurol. 193(1):85-100.
Polaski S, Whitney L, Barker BW, Stronach B. (2006) Genetic analysis of slipper/mixed lineage kinase reveals requirements in multiple Jun-N-terminal kinase-dependent morphogenetic events during Drosophila development. Genetics. 174(2):719-33.
Rämet M, Lanot R, Zachary D, Manfruelli P. (2002) JNK signaling pathway is required for efficient wound healing in Drosophila. Dev Biol. 241(1):145-56.
Ricos MG, Harden N, Sem KP, Lim L, Chia W. (1999) Dcdc42 acts in TGF-beta signaling during Drosophila morphogenesis: distinct roles for the Drac1/JNK and Dcdc42/TGF-beta cascades in cytoskeletal regulation. J Cell Sci. 112 (Pt 8):1225-35.
Riesgo-Escovar JR, Jenni M, Fritz A, Hafen E. (1996) The Drosophila Jun-N-terminal kinase is required for cell morphogenesis but not for DJun-dependent cell fate specification in the eye. Genes Dev. 10(21):2759-68.
Riesgo-Escovar JR, Hafen E. (1997a) Common and distinct roles of DFos and DJun during Drosophila development. Science. 1997 278(5338):669-72.
Riesgo-Escovar JR, Hafen E. (1997b) Drosophila Jun kinase regulates expression of decapentaplegic via the ETS-domain protein Aop and the AP-1 transcription factor DJun during dorsal closure. Genes Dev. 11(13):1717-27.

Roth P, Montell DJ. (1992) Drosophila C/EBP: a tissue-specific DNA-binding protein required for embryonic development. Genes Dev. 6(12A):2299-311.
Rubin GM, Yandell MD, Wortman JR, Gabor Miklos GL, Nelson CR, Hariharan IK, Fortini ME, Li PW, Apweiler R, Fleischmann W, Cherry JM, Henikoff S, Skupski MP, Misra S, Ashburner M, Birney E, Boguski MS, Brody T, Brokstein P, Celniker SE, Chervitz SA, Coates D, Cravchik A, Gabrielian A, Galle RF, Gelbart WM, George RA, Goldstein LS, Gong F, Guan P, Harris NL, Hay BA, Hoskins RA, Li J, Li Z, Hynes RO, Jones SJ, Kuehl PM, Lemaitre B, Littleton JT, Morrison DK, Mungall C, O'Farrell PH, Pickeral OK, Shue C, Vosshall LB, Zhang J, Zhao Q, Zheng XH, Lewis S. (2000) Comparative genomics of the eukaryotes. Science. 287(5461):2204-15.
Salvaing J, Mouchel-Vielh E, Bloyer S, Preiss A, Peronnet F. (2008) Regulation of Abd-B expression by Cyclin G and Corto in the abdominal epithelium of Drosophila. Hereditas. 145(3):138-46.
Sánchez L, Guerrero I. (2001) The development of the Drosophila genital disc. Bioessays. 23(8):698-707.
Seijffers R, Mills CD, Woolf CJ. (2007) ATF3 increases the intrinsic growth state of DRG neurons to enhance peripheral nerve regeneration. J Neurosci. 25;27(30):7911-20.
Shtil AA, Mandlekar S, Yu R, Walter RJ, Hagen K, Tan TH, Roninson IB, Kong AN. (1999) Differential regulation of mitogen-activated protein kinases by microtubule-binding agents in human breast cancer cells. Oncogene. 18(2): 377-84.
Sluss HK, Davis RJ. (1997) Embryonic morphogenesis signaling pathway mediated by JNK targets the transcription factor JUN and the TGF-beta homologue decapentaplegic. J Cell Biochem. 67(1):1-12.
Smolik SM, Rose RE, Goodman RH. (1992) A cyclic AMP-responsive element-binding transcriptional activator in Drosophila melanogaster, dCREB-A, is a member of the leucine zipper family. Mol Cell Biol. 12(9):4123-31.
Soares HD, Chen SC, Morgan JI. (2001) Differential and prolonged expression of Fos-lacZ and Jun-lacZ in neurons, glia, and muscle following sciatic nerve damage. Exp Neurol. 167(1):1-14.
Spradling AC, Rubin GM. (1982) Transposition of cloned P elements into Drosophila germ line chromosomes. Science. 218(4570):341-7.
Stewart HJ. (1995) Expression of c-Jun, Jun B, Jun D and cAMP response element binding protein by Schwann cells and their precursors in vivo and in vitro. Eur J Neurosci. 7(6):1366-75.
Stronach B, Perrimon N. (2002) Activation of the JNK pathway during dorsal closure in Drosophila requires the mixed lineage kinase, slipper. Genes Dev. 16(3):377-87.
Strutt DI, Weber U, Mlodzik M. (1997) The role of RhoA in tissue polarity and Frizzled signalling. Nature. 387(6630):292-5.
Suzanne M, Perrimon N, Noselli S. (2001) The Drosophila JNK pathway controls the morphogenesis of the egg dorsal appendages and micropyle. Dev Biol. 237(2):282-94.
Syed V, **Mukherjee** K, Lyons-Weiler J, Lau KM, Mashima T, Tsuruo T, Ho SM. (2005) Identification of ATF-3, caveolin-1, DLC-1, and NM23-H2 as putative antitumorigenic, progesterone-regulated genes for ovarian cancer cells by gene profiling. Oncogene. 24(10): 1774-87.
Talbot WS, Swyryd EA, Hogness DS. (1993) Drosophila tissues with different metamorphic responses to ecdysone express different ecdysone receptor isoforms. Cell. 73(7):1323-37.
Tamura K, Hua B, Adachi S, Guney I, Kawauchi J, Morioka M, Tamamori-Adachi M, Tanaka Y, Nakabeppu Y, Sunamori M, Sedivy JM, Kitajima S. (2005) Stress response gene ATF3 is a target of c-myc in serum-induced cell proliferation. EMBO J. 24(14):2590-601.
Taylor MD, Holdeman AS, Weltmer SG, Ryals JM, Wright DE. (2005) Modulation of muscle spindle innervation by neurotrophin-3 following nerve injury. Exp Neurol. 191(1):211-22.
Theodosiou NA, Xu T. (1998) Use of FLP/FRT system to study Drosophila development. Methods. 14(4):355-65.
Thummel CS. (1996) Files on steroids--Drosophila metamorphosis and the mechanisms of steroid hormone action. Trends Genet. 12(8):306-10.
Thummel CS. (2001) Steroid-triggered death by autophagy. Bioessays. 23(8):677-82.
Toyama Y, Peralta XG, Wells AR, Kiehart DP, Edwards GS. (2008) Apoptotic force and tissue dynamics during Drosophila embryogenesis. Science. 321(5896):1683-6.
Tsujino H, Kondo E, Fukuoka T, Dai Y, Tokunaga A, Miki K, Yonenobu K, Ochi T, Noguchi K. (2000) Activating transcription factor 3 (ATF3) induction by axotomy in sensory and motoneurons: A novel neuronal marker of nerve injury. Mol Cell Neurosci. 15(2):170-82.
Tsuzuki K, Kondo E, Fukuoka T, Yi D, Tsujino H, Sakagami M, Noguchi K. (2001) Differential regulation of P2X(3) mRNA expression by peripheral nerve injury in intact and injured neurons in the rat sensory ganglia. Pain. 91(3):351-60.

Turchi L, Aberdam E, Mazure N, Pouysségur J, Deckert M, Kitajima S, Aberdam D, Virolle T. (2008) Hif-2alpha mediates UV-induced apoptosis through a novel ATF3-dependent death pathway. Cell Death Differ. 15(9):1472-80.
Usui T, Smolik SM, Goodman RH. (1993) Isolation of Drosophila CREB-B: a novel CRE-binding protein. DNA Cell Biol. 12(7):589-95.
von Kalm L, Fristrom D, Fristrom J. (1995) The making of a fly leg: a model for epithelial morphogenesis. Bioessays. 17(8):693-702.
Ward RE, Reid P, Bashirullah A, D'Avino PP, Thummel CS. (2003) GFP in living animals reveals dynamic developmental responses to ecdysone during Drosophila metamorphosis. Dev Biol. 256(2):389-402.
Wolfgang CD, Chen BP, Martindale JL, Holbrook NJ, Hai T. (1997) gadd153/Chop10, a potential target gene of the transcriptional repressor ATF3. Mol Cell Biol. 17(11):6700-7.
Xu J, Wang F, Van Keymeulen A, Herzmark P, Straight A, Kelly K, Takuwa Y, Sugimoto N, Mitchison T, Bourne HR. (2003) Divergent signals and cytoskeletal assemblies regulate self-organizing polarity in neutrophils. Cell. 114(2):201-14.
Yin T, Sandhu G, Wolfgang CD, Burrier A, Webb RL, Rigel DF, Hai T, Whelan J. (1997) Tissue-specific Pattern of Stress Kinase Activation in Ischemic/Reperfused Heart and Kidney. J. Biol. Chem. 272: 19943.
Yin VP, Thummel CS. (2004) A balance between the diap1 death inhibitor and reaper and hid death inducers controls steroid-triggered cell death in Drosophila. Proc Natl Acad Sci U S A. 101(21):8022-7.
Yin VP, Thummel CS, Bashirullah A. (2007) Down-regulation of inhibitor of apoptosis levels provides competence for steroid-triggered cell death. J Cell Biol. 178(1):85-92.
Yin X, Dewille JW, Hai T. (2008) A potential dichotomous role of ATF3, an adaptive-response gene, in cancer development. Oncogene. 27(15):2118-27.
Yoshida T, Sugiura H, Mitobe M, Tsuchiya K, Shirota S, Nishimura S, Shiohira S, Ito H, Nobori K, Gullans SR, Akiba T, Nitta K. (2008) ATF3 protects against renal ischemia-reperfusion injury. J Am Soc Nephrol. 19(2):217-24.
Zahedi B, Shen W, Xu X, Chen X, Mahey M, Harden N. (2008) Leading edge-secreted Dpp cooperates with ACK-dependent signaling from the amnioserosa to regulate myosin levels during dorsal closure. Dev Dyn. 237(10):2936-46.
Zeitlinger J, Kockel L, Peverali FA, Jackson DB, Mlodzik M, Bohmann D. (1997) Defective dorsal closure and loss of epidermal decapentaplegic expression in Drosophila fos mutants. EMBO J. 16(24):7393-401.
Zeitlinger J, Bohmann D. (1999) Thorax closure in Drosophila: involvement of Fos and the JNK pathway. Development. 126(17):3947-56.
Zhang K, Chaillet JR, Perkins LA, Halazonetis TD, Perrimon N. (1990) Drosophila homolog of the mammalian jun oncogene is expressed during embryonic development and activates transcription in mammalian cells. Proc Natl Acad Sci U S A. 87(16):6281-5.
Zhang C, Kawauchi J, Adachi MT, Hashimoto Y, Oshiro S, Aso T, Kitajima S. (2001) Activation of JNK and transcriptional repressor ATF3/LRF1 through the IRE1/TRAF2 pathway is implicated in human vascular endothelial cell death by homocysteine. Biochem Biophys Res Commun. 289(3): 718-24.
Zhou X, Riddiford LM. (2002) Broad specifies pupal development and mediates the 'status quo' action of juvenile hormone on the pupal-adult transformation in Drosophila and Manduca. Development. 129(9):2259-69.