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REVIEWS

# Morphogenetic Networks which Determine the Spatial Expression of Zygotic Genes in Early *Drosophila* Embryo

**S. Yu. Surkova[a], E. V. Golubkova[b], L. A. Mamon[b], and M. G. Samsonova[a]**

[a] *St. Petersburg Polytechnic University, Mathematical Biology and Bioinformatics Laboratory, ul. Politekhnicheskaya 29, St. Petersburg, 195251 Russia*

[b] *St. Petersburg State University, Department of Genetics and Biotechnology, Universitetskaya nab. 7/9, St. Petersburg, 199034 Russia*

*e-mail: surkova.spb@mail.ru*

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**Abstract**—This review deals with the recent studies expanding the idea of positional information in the early embryogenesis of *Drosophila melanogaster*. Previous studies showed that, in the course of segment determination in *Drosophila,* information created by gradients of products of maternal coordinate genes is not "read" statically, being interpreted by their zygotic target genes via regulatory interactions. This leads to spatial shifts in the expression of target genes relative to the original positions as well as to dynamic reduction in the zygotic expression variability. However, according to recent data, interpretation of positional information includes the interaction between not only zygotic target genes but also the maternal coordinate genes themselves. Different systems of maternal coordinate genes (maternal systems)—the posterior-anterior, terminal, and dorsoventral—can interact with each other. This is usually expressed in the regulation of zygotic target genes of one maternal system by other maternal systems. The concept of a "morphogenetic network" was introduced to define the interaction of maternal systems during determination of spatial gene expression in the early *Drosophila* embryo.

*Keywords*: maternal gradients, positional information, morphogenesis, *Drosophila* embryo, segmentation, Bicoid, Torso

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## INTRODUCTION

At the early stages of embryonic development of multicellular organisms, individual cells receive information about their position in the embryo by interpreting the concentrations of transcription factors or signaling molecules, which form a morphogenetic gradient (Gurdon and Bourillot, 2001; Tabata and Takei, 2004). There are two main concepts on the nature of interpretation of such gradients of target genes (Liu et al., 2013). The first concept is based on the classic "French flag model" by Lewis Wolpert (1969). According to this concept, the threshold concentrations of morphogenetic gradients provide all necessary spatial information for the expression of target genes and, later, for the formation of the corresponding structure of the developing organism. According to the second concept, gradients implement only an instructing role, and the positional information created by them is greatly refined in the future by cross-regulation in the networks of target genes.

*Drosophila melanogaster* embryo is a very convenient model for studying the effect of maternal gradients. In the early embryo, the spatial coordinates are set by the systems of maternal coordinate genes (maternal systems), which function along the anteroposterior (A-P) and dorsoventral (D-V) axes of the embryo. Information set by these systems is then interpreted by zygotic genes. The maternal systems functioning along the A-P axis are divided into the anterior, posterior, and terminal systems.

The anterior maternal system is represented by a concentration gradient of the Bicoid transcription factor (Bcd) with a maximum on the anterior pole of the embryo, where *bcd* mRNA is localized (Frohnhofer and Nusslein-Volhard, 1986; Driever and Nusslein-Volhard, 1988a). The Bcd protein is distributed nearly along the entire A-P axis and affects the spatial expression of numerous target genes (Fig. 1a). It should be noted that Bcd exhibits the properties of a classic morphogen: the the expression domains of zygotic target genes of Bcd are shifted along the A-P axis depending on the *bcd* dose in the embryo. When *bcd* doses increase, the expression pattern of the target genes are shifted posteriorly, whereas a decrease in *bcd* doses causes a shift in the anterior direction (Driever and Nusslein-Volhard, 1988b; Namba et al., 1997). Thus, it can be postulated that the positions of these domains depend on the threshold levels of Bcd concentration. Lewis Wolpert used this property of the Bcd gradient

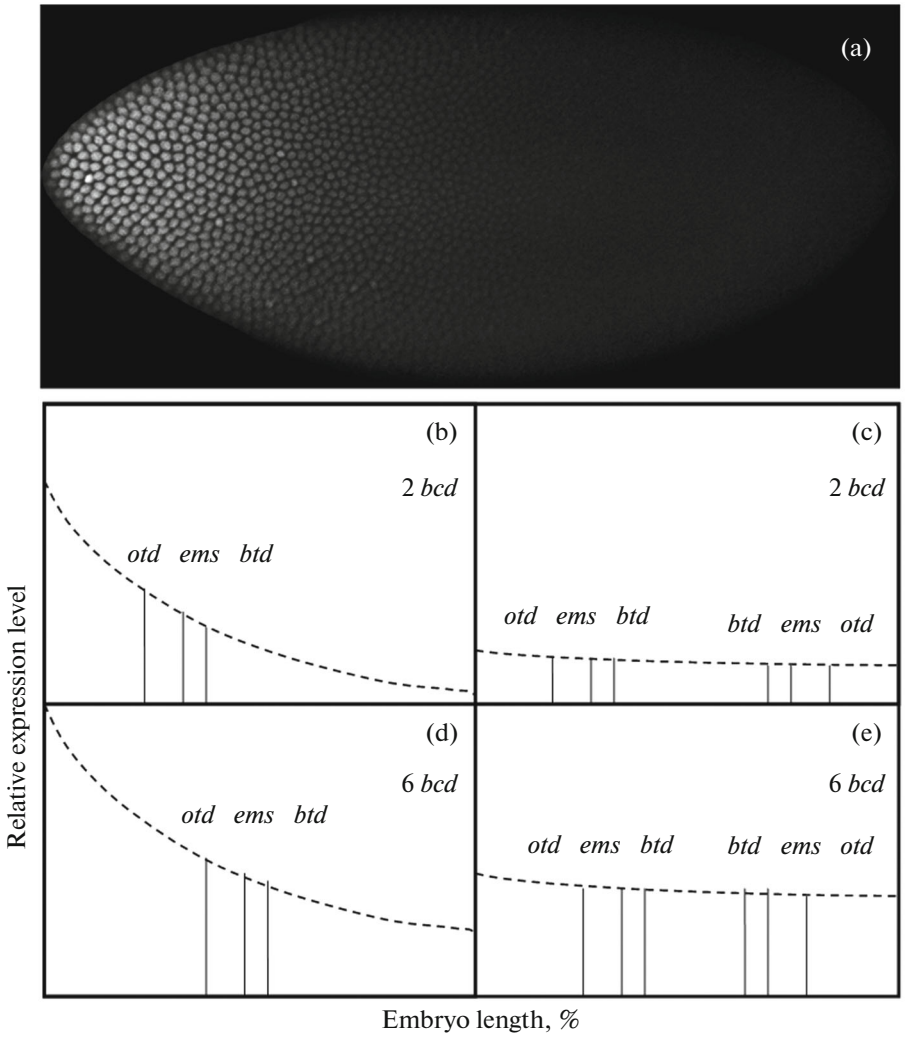


**Fig. 1.** Effect of changes in the Bcd concentration on the formation of expression boundaries of the target genes in *Drosophila melanogaster*. (a) Image of the *bcd* expression pattern in the wild-type embryo retrieved from the FlyEx database (http://urchin.spbcas.ru/flyex/) (Pisarev et al., 2009). Schematically are shown the relative positions and the A-P positions of the expression boundaries of the anterior target genes of Bcd, such as *otd*, *ems,* and *btd* in (b) wild-type embryo, (d) embryo carrying six copies of the *bcd* gene, (c) embryo with a homogeneous distribution of the Bcd protein, and (e) embryo with a homogeneous distribution of the Bcd protein carrying six copies of the *bcd* gene (Ochoa-Espinosa et al., 2009).

as an illustration of the French flag model. However, more recent findings have made changes in this model and showed that the reading of the positional information from the Bcd gradient by zygotic genes targets is not passive and requires interactions between these target genes. It was found that, after the initialization of expression domains of zygotic gap genes and pair-rule genes, their A-P positions are refined, which is manifested in shifting and narrowing the expression domains of these genes, as well as in reducing their spatial variability over time. Experiments *in silico* showed that, in the interaction network of gap genes, such processes are determined by mutual regulation of these genes (Jaeger et al., 2004a; Surkova et al., 2008a, 2008b, 2011; Manu et al., 2009).

The posterior maternal system in *Drosophila* embryos is represented by the Nanos (Nos) protein, whose function is to form the A-P gradient of the maternal transcription factor Hunchback (Hb). The latter, together with Bcd, is involved in establishing the expression boundaries of abdominal gap genes (Lehmann and Akam, 1989; Yu and Small, 2008; Porcher et al., 2010; Jaeger 2011). The terminal system is responsible for the formation of terminal structures of the embryo—the acronym and the telson. This is a signaling pathway, whose key component is the Torso (Tor) tyrosine kinase receptor (Weigel et al., 1990). Tor activates the expression of zygotic genes at the poles of the embryo via indirect mechanisms based on repression of the repressors. In particular, the activity of a homogeneously distributed maternal repressor

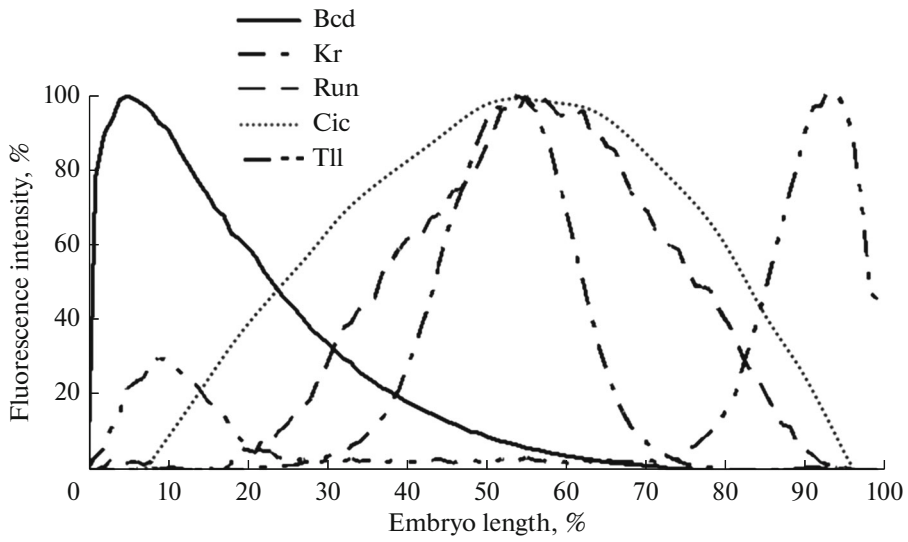


**Fig. 2.** Repressors that determine the boundaries of Bcd target genes in *Drosophila melanogaster*. The averaged expression patterns of *bcd*, *run,* and *Kr* genes for the beginning of cycle 14A (time class 1) from the FlyEx database are presented (Pisarev et al., 2009). The expression region of the *cic* gene is represented schematically in accordance with the data by Chen et al. (2012). The expression of the terminal gap gene *tll* at the poles of the embryo is also shown. The *hkb* gene is expressed similarly. In the center of the embryo, the expression of *tll* and *hkb* is repressed by Cic.

Capicua (Cic) remains maximum in the center of the embryo, allowing the terminal genes, such as *tailless* (*tll*) and *huckebein* (*hkb*), to be expressed on the poles (Fig. 2) (Jimenez et al., 2000).

The spatial expression of zygotic genes along the D-V axis in *Drosophila* embryos depends on the gradient of Dorsal (Dl), which is a transcription factor and regulates more than 50 target genes (Stathopolulos and Levine, 2002).

Using Bcd as an example, it was shown that maternal gradients play an instructing rather than a decisive role in the formation of spatial expression of target genes, which is then refined via interactions in zygotic gene networks. Nevertheless, the results of a number of studies indicate that maternal systems in the embryo can interact with one another.

For example, it was shown that the maternal terminal system (Tor) together with Bcd is responsible for the formation of gene expression patterns in the head region of the embryo. The interaction of Bcd and Tor may be either synergistic or antagonistic. Tor cascade and Bcd gradient can independently activate the expression of terminal genes, such as *hkb*. Interestingly, this function of Tor can be redundant, because head defects observed in null *tor* mutants can be abolished at high concentrations of Bcd (Schaeffer et al., 2000). In addition, there is a hypothesis that the Tor phosphorylates Bcd (Ronchi et al., 1993), thereby enhancing its morphogenetic function along the A-P axis (Gao et al., 1996; Janody et al., 2000). At the same time, at the anterior pole of the embryo, Tor can have a negative impact on Bcd, leading to the repression of genes such as *hb* and *orthodenticle* (*otd*) (Ronchi et al., 1993; Bellaïche et al., 1996).

This review considers recent studies in which the mechanisms underlying the interaction between different maternal systems in the early *Drosophila* embryo were investigated. To define the interactions of maternal systems in determining the spatial expression of zygotic genes, the concept of a "morphogenetic network" was introduced (Lohr et al., 2009, 2010). It is obvious that the effect of a morphogenetic network as a mechanism of interpretation of spatial information should be further studied.

## INTERACTION OF BCD AND THE TERMINAL SYSTEM IS REQUIRED TO ESTABLISH THE SPATIAL GENE EXPRESSION IN THE ANTERIOR REGION

In 2009, two groups of researchers published the results of experiments that, firstly, largely clarified the role of Bcd as a morphogen and, secondly, revealed the mechanisms of its interaction with the genes of the terminal system (Ochoa-Espinosa et al., 2009; Lohr et al., 2009). In these experiments, embryos in which the Bcd protein was distributed almost homogeneously along the A-P axis without forming a concentration gradient were created (Ochoa-Espinosa et al., 2009). Thus, the French flag model, in which the threshold concentrations of the morphogenetic gradient determine the positions of expression regions of the target genes, does not work in this experimental system.

This made it possible to test whether the expression of the target genes of Bcd, indeed, strongly depends on the threshold concentrations of the gradient and whether Bcd is the only morphogen functioning in the anterior area. If the initial A-P positions of the target genes of Bcd are determined solely by the threshold concentrations, then the embryos with a homogeneous distribution of the Bcd protein will have no precise localization of the expression regions of the target genes and their relative position will change.

These experiments gave unexpected results: in the embryos with a homogeneous distribution of the Bcd protein, the anterior target genes of Bcd, such as *otd*, *empty spiracles* (*ems*), and *buttonhead* (*btd*) formed spatially distinct expression domains and, most importantly, retained their relative positions along the A-P axis (Figs. 1b, 1c) (Ochoa-Espinosa et al., 2009).

When the Bcd dose increased by a factor of 3, the boundaries of the expression regions of the target genes were shifted to the center of the embryo but remained quite clear (Figs. 1d, 1e). This fact suggests that the sensitivity of the regulatory elements to different Bcd concentrations is not the main mechanism that ensures the formation of the boundaries of expression regions of the target genes along the A-P axis (Ochoa-Espinosa et al., 2009).

Another important result of these experiments was that, in the embryos with a homogeneous distribution of Bcd, the anterior expression of target genes is duplicated in a mirror reflection in the posterior part of the embryo (Figs. 1c, 1d) (Ochoa-Espinosa et al., 2009). In this connection, the authors assumed that the expression of these genes may depend on the terminal system, which is consistent with the results of previous studies (Wimmer et al., 1995; Gao et al., 1996).

The mechanism of action of the terminal system on the positioning of Bcd target genes was studied by Lohr et al. (2009). The effect of mutations in the terminal-system genes on the positioning of Bcd target genes was studied in the UASp/Gal4 system with a homogeneous distribution of the Bcd protein.

The maternal repressor Cic is regulated by the Tor signaling cascade so that a high Cic concentration is retained in the center of the embryo but decreases towards its poles (Fig. 2). It was found that the positions of the expression domains of Bcd target genes in the anterior part (*giant* (*gt*), *hkb*, *knirps* (*kni*), *otd*, *slp2*, *ems*, and *cap-n-collar* (*cnc*)) depend on the activity of Cic (Lohr et al., 2009). Cic may exercise repression through specific binding sites in the Bcd-dependent enhancer and is an antagonist of the Bcd-mediated gene activation.

However, the effect of Cic is limited to the anterior region, whereas in the posterior half of the embryo (60–100% of the embryo length) the boundaries of expression domains of Bcd target genes are presumably determined by other (Tor-dependent) genes.

Experiments with a homogeneous distribution of the Bcd protein also showed that the Bcd concentration in the anterior part of the embryo is higher than the concentration required for target gene activation (Ochoa-Espinosa et al., 2009). Since the anterior expression of genes such as *cns* and *gt* in the absence of Cic extends more posteriorly (Fig. 3), it was hypothesized that, in the anterior part of the embryo, Bcd activates the target genes in the form of broad regions, which are then determined more precisely by Cic and other repressors (Lohr et al., 2009).

## SYSTEM OF REPRESSORS ESTABLISHING THE BOUNDARIES OF EXPRESSION OF BCD TARGET GENES

On the basis of the above results, which showed that the expression of the target genes of Bcd can be activated at much lower concentrations of the latter than those detected in the wild-type embryo (Ochoa-Espinosa et al., 2009), it was assumed that there exists a whole system of repressors that set the boundaries of expression regions of Bcd target genes (Chen et al., 2012). In addition to the maternal repressor Cic, a terminal-system component, this role may be played by the gap gene *Krüppel* (*Kr*), which sets the boundaries of the anterior stripes of pair-rule gene—*even skipped* (*eve*) and *sloppy paired 1* (*slp1*) (Small et al., 1991; Stanojevic et al., 1991; Andrioli et al., 2004). Another possible candidate for the role of the Bcd antagonist was the pair-rule gene *runt* (*run*). Earlier, it was established that the *run* gene exhibits the properties of the gap gene. The ectopic *run* expression in the entire embryo changed the expression pattern of the abdominal and head gap genes (Tsai and Gergen, 1994).

Importantly, in the early embryo, *Kr* and *run*, similarly to *cic*, are expressed in the form of wide regions with a maximum in the center, decreasing towards the poles of the embryo (Fig. 2).

Chen et al. (2012) analyzed 66 Bcd-dependent regulatory elements and showed that, indeed, the boundaries of their expression domains are positioned by repressor gradients directed oppositely to the Bcd gradient. It was demonstrated experimentally that Run plays the key role and functions together with Cic and Kr.

For example, the boundaries of the anterior expression domains of Bcd target genes, such as *otd*, *slp1*, and *gt*, in single mutants for *cic* or *run* were considerably shifted posteriorly (Fig. 3), but the order of their relative position did not change. Conversely, in the double mutants *run; cic* all three expression boundaries were fused, which led to radical defects in the head formation. Since the Bcd gradient in these double mutants did not change, this finding is evidence that the correct positioning of the Bcd-dependent expression boundaries requires a combined action of repressors (Chen et al., 2012). Interestingly, the repressors that are involved in the positioning of

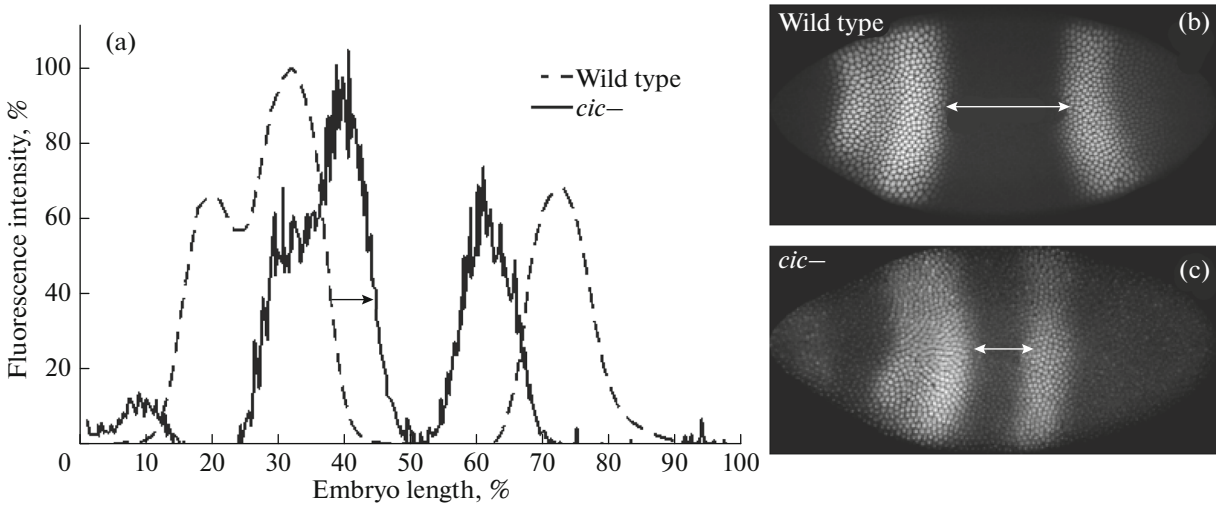


**Fig. 3.** Significant shift in the expression domains of *gt*, a target gene of Bcd, in the null- mutants for the maternal terminal gene *cic*. (a) Quantitative data and images of expression patterns of the *gt* gene in (b) wild-type embryos from the FlyEx database (Pisarev et al., 2009) and the (a, c) null mutants for the maternal repressor *cic* (our data) for the time class 6 of cycle 14A are shown. The black arrow in panel (a) marks the shift of the anterior *gt* expression in the *cic*– embryos compared to the wild-type embryos, and the white arrows in panels (b) and (c) shows the decrease in the distance between the anterior and posterior *gt* expression regions in the *cic*– embryos.

the boundaries of Bcd target genes are represented by different classes of genes: the maternal terminal gene *cic* and two zygotic A-P genes *Kr* and *run*, belonging to different classes differe gap and pair-rule, respectively.

## SPATIAL SHIFTS IN EXPRESSION REGIONS IN EMBRYOS WITH ALTERED BCD CONCENTRATION DEPEND ON THE TERMINAL AND POSTERIOR SYSTEMS

As mentioned earlier, the classical proof of the morphogenic role of the Bcd gradient is the shift in the expression pattern of the target genes depending on the *bcd* dose in the embryo. When the *bcd* dose increases, the head furrow shifts posteriorly and the region of the segmental germ band narrows, because the anterior expression regions of the target genes in the area with the highest Bcd concentration are shifted most significantly. Accordingly, when the *bcd* dose decreases, the expression regions of the target genes are shifted anteriorly, and the region of segmental germinal band broadens (Driever and Nusslein-Volhard, 1988b; Namba et al., 1997).

Liu et al. (2013) studied the pattern shift dynamics depending on the Bcd concentration rather than on the number of *bcd* copies in the maternal genome. For this purpose, transgenic *Drosophila* strains with different absolute levels of *bcd* expression were created (Liu et al., 2013). The results showed that, in the early embryo, the A-P positions of the target genes are shifted in exact accordance with the degree of change in the Bcd concentration; however, later the system is partially adapted to the changed Bcd level, and the expression domains of the target genes are shifted back towards their positions in the wild-type embryo. Thus, the effect of increased Bcd concentration in the embryo is compensated due to certain regulatory mechanisms.

This effect was not observed when similar measurements were performed in the embryos with altered Bcd levels that were mutant for other mutant maternal factors—*torso-like* (*tsl*) and *nos*. The *tsl* gene is a component of the terminal system and is responsible for the Tor receptor activation, and the *tsl* knockout blocks the Tor function. Thus, in this case, the dynamics of the positioning of Bcd target genes depends on the action of genes representing the posterior and terminal maternal systems. Interestingly, the integration of interactions of these systems is not reached initially, during the formation of the boundaries of the expression domains of the zygotic of genes under the influence of maternal factors, but occurs during the embryonic development.

Earlier studies showed that, in the wild-type embryos, the expression domains of gap and pair-rule genes in the posterior part of the embryo were dynamically shifted after their initial positioning by the maternal gradients (Fig. 4a) (Jaeger et al., 2004a; Surkova et al., 2008). These dynamic changes were caused by the asymmetric repression between the zygotic genes themselves; the genes that are expressed more posteriorly repress the genes that are expressed more anteriorly but not vice versa (Jaeger et al., 2004a, 2004b).

As can seen from the results of studies by Liu et al. (2013), the positional dynamics of the expression of

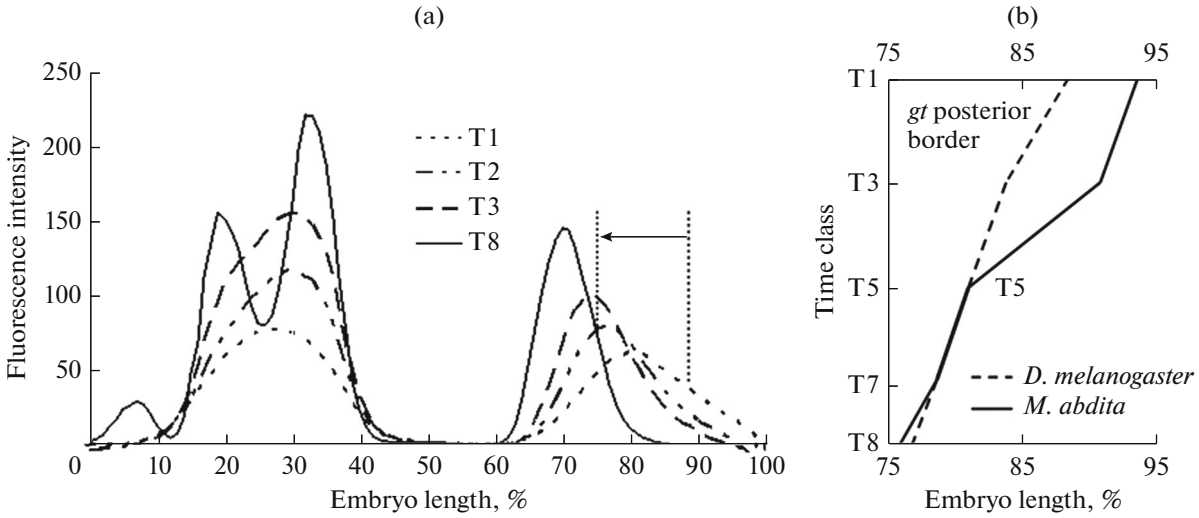


**Fig. 4.** Dynamic shift in the posterior expression domain of the *gt* gene in the course of development in *D. melanogaster* and *M. abdita*. (a) The arrow shows the spatial shift of the posterior expression region of the *gt* gene in *D. melanogaster* in cycle 14A of the wild-type embryo from the FlyEx database (Pisarev et al., 2009). (b) The posterior boundary of the *gt* expression domain in *M. abdita* at the beginning of cycle 14A is located much closer to the posterior pole of the embryo than in *D. melanogaster*. However, by the time class 5 (T5), the position of this boundary in the two species coincide due to a stronger shift in the *gt* expression domain in *M. abdita* (shown schematically according to Wotton et al., 2015a).

Bcd target genes may also depend on other maternal factors.

## HIGHER CONCENTRATIONS OF MORPHOGEN REQUIRE MORE INTENSIVE INTERPRETATION

From the evolutionary point of view, it would be important to establish the mechanisms of interpretation of the effect of anterior morphogens in other insects. Bcd is unique to the order Diptera. In recent years, in addition to *Drosophila,* its role in development was studied in the scuttle fly *Megaselia abdita*, which is more primitive than *Drosophila*. A characteristic feature of establishment of positional information in *M. abdita* is a much higher level of the Bcd gradient than in *Drosophila*. The Bcd gradient in the wild-type *Megaselia* embryos is similar in intensity to that characteristic of *Drosophila* embryos with an increased number of *bcd* copies in the genome. The loss of the *bcd* function leads not only to the absence of head and thoracic structures, as is observed in *Drosophila*, but also to the deletion of three or four abdominal segments (Stauber et al., 2000).

In a recent paper, Wotton et al. (2015a) considered the interpretation of positional information in an early *M. abdita* embryo at the level of zygotic gap genes. An elevated Bcd level naturally leads to a posterior shift in the expression patterns of the target genes compared to their A-P positions in the *Drosophila* embryo (Fig. 4b). As described above, during *Drosophila* embryo development, the expression domains of gap genes were shifted anteriorly due to mutual repression by these genes (Fig. 4a) (Jaeger et al., 2004a, 2004b; Surkova et al., 2008) Interestingly, in *M. abdita,* these shifts were much more profound and, as a result, the posterior boundaries of the expression regions of abdominal gap genes over time came to the same spatial coordinates as in *D. melanogaster* (Fig. 4). However, in the case of *M. abdita*, this requires a stronger repression in interactions between gap genes (Wotton et al., 2015a).

If, even in *Drosophila,* the level of Bcd exceeds the level that is required for target gene activation, the Bcd concentration in *M. abdita* is initially substantially elevated. This is probably due to the lack of maternal gradient of Cad in the posterior part; as a result, the anterior morphogen has to function as an activator of zygotic expression in the posterior part of the embryo (Wotton et al., 2015b).

A detailed analysis of all maternal factors involved in establishment of positional information in *M. abdita* has not yet been performed. However, it would be interesting to reveal the mechanisms of establishing the spatial expression of the anterior target genes of Bcd (for example, those shown in Fig. 1b for *D. melanogaster*) at such a high level of its concentration.

## TERMINAL SYSTEM IS INVOLVED IN THE REGULATION OF THE DORSOVENTRAL PATTERNING

It should be noted that interactions of maternal system were identified not only along the A-P axis of the embryo. For example, Helman et al. (2012) described the mechanism of interaction of the Tor signaling cascade with the Dorsal (Dl) gradient, which determines

the formation of spatial gene expression along the D-V axis. Dl is a transcription factor. Depending on the Dl level, the embryo is divided into three germ layers—the mesoderm, the neuroectoderm, and the dorsal ectoderm (Reeves and Stathopoulos, 2009). Previously, it was shown that Tor controls the expression of Dl target genes at the poles of the embryo (Rush and Levine, 1994). Recent studies have shown that Tor signaling pathway influences the Dl gradient per se. By switching off the effect of repressors Cic and Gro, Tor induces the expression of the *wnt inhibitor of Dorsal* (*wntD*) gene, which belongs to the family of Wingless/Wnt signaling factors. The latter represses the Dl gradient in nuclei and the expression of its target genes at the poles of the embryo (Helman et al., 2012).

## NONCODING RNAs AS COMPONENTS OF MORPHOGENETIC NETWORKS

Recent studies have shown that microRNA are an important component of the regulatory networks that control gene expression. It was found that, in an early *Drosophila* embryo, transcription factors interact with microRNA and that the microRNA expression is regulated by tissue-specific enhancers similar to those of the genes encoding proteins (Biemar et al., 2005). It was shown that the RNA precursor of the miR-309 cluster is activated by the transcription factor Zelda (Zld; **Z**ink-finger **e**ar**l**y **D**rosophila **a**ctivator) (Liang et al., 2008; Fu et al., 2014). Despite the fact that Zld is expressed homogeneously throughout the embryo, the miR-309 transcript activated by this factor is expressed inhomogeneously along the A-P axis of the embryo. It was found that Bcd, similarly to Zelda, have regulatory effects on the miR-309 enhancer. It was assumed that miR-309 is first activated by Zld and then by other Bcd-dependent factors (Fu et al., 2014). In addition, it was hypothesized that miR309 in the terminal areas of the embryo is regulated by a terminal system, namely, by the *hkb* gene, a zygotic target of the Tor cascade (Biemar et al., 2005; Fig. 2). Thus, the results indicate that miRNA regulation may involve components of different maternal systems functioning in the early *Drosophila* embryogenesis.

## CONCLUSIONS

This review considers the results of studies demonstrating the role of interactions of maternal systems in the establishment of positional information in the embryogenesis of the model object, the fruit fly *Drosophila*.

In the early *Drosophila* embryo, the major morphogen is Bcd, an anterior gradient distributed nearly along the entire A-P axis of the embryo. There are evidences confirming that the precise positioning of Bcd target genes requires additional regulators. A question arises as to whether all morphogenetic gradients require additional interpretation mechanisms. Chen et al. (2012) assumed that this may depend on the number of boundaries of expression regions set by the gradient. For example, it was shown that the extracellular signaling protein activin activates the target genes depending on its concentration in isolated animal parts of frog embryos (Gurdon et al., 1998). At the same time, the Decapentaplegic (Dpp) signal forms an activity gradient in the wing imaginal disc of *Drosophila,* which is then refined through interactions with many extracellular factors (Affolter and Basler, 2007).

Data presented in this review, which describe the characteristics of formation of the gene expression pattern in embryogenesis of the scuttle fly *Megaselia,* indicate that a more intensive interpretation of a maternal gradient may be required in the case of its excess concentration at the same number of target gene boundaries.

The study of the mechanisms of establishment of positional information in different insects has not yet been performed in full scale at the level of gene networks. However, in general, the results indicate that the important role of the anterior morphogen in evolution has been retained. It should be noted that a conserved function of the anterior morphogen has been revealed despite the absence of its conservatism at the molecular level. For example, in the insect *Nasonia*, which represents the transition from the type of development with a short germ band to the development with a long germ band, the role of Bcd is played by *otd*, an ortholog of the head gap gene in Diptera (Rosenberg et al., 2009). The Otd homeodomain can bind to the same sequence as Bcd (Treisman, 1989; Weisbrod et al., 2013). Interestingly, the *otd* gene in *Drosophila* is the target gene of Bcd, as it is described described in this review. At the same time, in the mosquito *Chironomus,* the role of the anterior morphogen is implemented by the *panish* gene product, which has a different type of the DNA-binding domain than Bcd—the so-called C-clamp domain (Klomp et al., 2015).

In addition, data described in this review emphasize the role of the terminal system in establishment of spatial information in the *Drosophila* embryo. Terminal genes interact with both the anteroposterior and dorsoventral maternal systems and are also involved in the regulation of microRNAs. This may be a consequence of the important role that the terminal system presumably played in the course of evolution, coordinating the posterior growth zone in the insects with a short germ band (Weisbrod et al., 2013).

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