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REVIEWS

Neural regulation of body polarities in nereid worm regeneration

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Abstract

Nerve dependence in regeneration has been established more than 200 years ago but the mechanisms by which nerves are necessary to regeneration remain to be fully elucidated. Aside from their direct impact in stimulating cellular growth, nerves also have a role on the establishment of body polarities (antero-posterior and dorso-ventral patterns) and this has been particularly well studied in nereid annelid worms. Nereids can regenerate appendages (parapodia) and the tail (body segments). In both parapodia and tail regeneration, the presence of the nerve cord is necessary to the establishment of body polarities. In this review, we will detail the experimental procedures which have been conducted in nereids to elucidate the role of the nerve cord in the establishment of the antero-posterior and dorso-ventral polarities. Most of the studies reported here were published several decades ago and based on anatomical and histological analyses; this review should constitute a knowledgebase and an inspiration for needed modern-time explorations at the molecular levels to elucidate the impact of the nervous system in the acquisition of body polarities.

KEYWORDS

annelids, body polarity, nerve, positional information, regeneration

1 | INTRODUCTION

While animal regeneration was discovered and studied by pioneer biologists from the beginning of the 18th century,[1] the role of nerves was first shown by Todd in 1823[2] who observed that denervation of an amputated limb in the newt inhibited its regeneration. This nerve dependence was then largely confirmed in a series of regenerating animals, especially in invertebrates, which are more prone to regeneration. It is now established that nerves exert their action through mitogenic factors whose nature is still unclear despite continuous scientific effort.[3] Nevertheless, it has also been shown that the production of nerve mitogens is linked to nerve regeneration, as growing neurites play an essential function in stimulating the regenerate.[4,5] Recently, nerve dependence was also described in cancer, a situation similar to regeneration in the sense that both, regeneration and cancer, need a supply of new cells.[6]

Abbreviations: Admp, antidorsalizing morphogenetic protein; AP, antero-posterior; BMP, bone morphogenetic protein; DV, dorso-ventral; SAZ, segment addition zone.

This article is dedicated to the memory of Professor Charles H. Taban (M.D.) of Geneva (1925–2020) who pursued regeneration research all his life, from his early studies under Emile Guyénot in Paris and in his own laboratory in Geneva, until his death on 29 November, 2020.

Cancer initiation, progression and metastasis are stimulated by the presence of nerves infiltrated in the tumor microenvironment,[7–9] emphasizing the importance of the neural tissue in both regeneration and cancer.[6]

Aside from nerve dependence, it was demonstrated that regeneration also stems from the juxtaposition of tissues normally distant from each other that become in contact after amputation, creating a positional discontinuity. Positional discontinuity will be compensated by regeneration whose finality appears to restore a positional continuity.[10,11] This morphogenic response has been well described in newt during limb regeneration[12] but also in other animal models.[13] Importantly, nerves and positional discontinuity represent the two required conditions for regeneration. Only one of these conditions is not sufficient for regeneration as the deviation of a nerve to a non-competent area (i.e., without positional discontinuity) can initiate at most a little outgrowth but never a normal regenerate.[3] Conversely, a positional discontinuity without regenerating nerve fibers is ineffective for a normal regeneration process.[3]

In this review, we detail the experimental protocols which have been implemented to demonstrate the role of nerves and the nerve cord in the regeneration of the nereid worms. These anatomical and histological experimentations have been largely forgotten but they nevertheless provide clues in relation to the trophic role of the nervous system that could be applicable to better understand the role of nerves in other animal models of regeneration and potentially in cancer.

2 | NEREIDS AS A REGENERATION MODEL

Many invertebrates are characterized by high regeneration capacities, especially planarians and annelids worms. Polychaete annelid worms, and in particular the nereids, are easy to experiment with, and existing genomic data make it a model of renewed interest for tail regeneration.[14] The body of Nereidae (Figure 1A) is a long chain of segments largely similar along the body between two terminal parts, the prostomium (fused with the peristomium, corresponding in part to the first segment, to form the head with the mouth) anteriorly, and the pygidium with the anus posteriorly, both representing the two parts of the young trochophore larva. All segments, at the exception of the prostomium, peristomium, and pygidium bear a pair of lateral appendages called parapodia. Parapodia are essentially used for locomotion through paddles and setae, giving the name of setigerous segments to these differentiated segments (Figure 1B). These setigerous segments, corresponding to metameres, are constantly produced postero-anteriorly from a proliferative zone (called the segment addition zone, SAZ) adjacent to the pygidium. These segments appear early in development, during the metamorphosis of the trochophore larva, and the production of new segments continues during the entire lifespan of the worm but stops correlatively with sexual maturation, ending to worm death after spawning. After tail amputation, regeneration follows the same plan as normal growth, giving to the regenerate a typical antero-posterior (AP) pattern (i.e. conical shape). During growth and regeneration, the new segments built from the SAZ will differentiate parapodia, innervated by parapodial nerves issued from the segmental ganglia lined along the ventral nerve cord. Parapodia are the first morphological criteria of segment differentiation and are characterized by their dorso-ventral (DV) pattern; their morphological details (cirri length, composition of bristles bundles, bristle, and paddle morphology) can be used as markers of polarity. The DV polarity of these setigerous segments is also clear because of the pigmentation of their dorsal side. Anatomically, the presence of the unique mid-ventral nerve cord is the first obvious feature of the ventral identity, as shown in a transversal section (Figure 1C).

3 | PARAPODIA VS SEGMENT REGENERATION IN NEREIDS

Parapodia regenerate easily after amputation, but supernumerary parapodia can be induced when a piece of latero-dorsal tegument is grafted on the latero-ventral tegument of the intact worm and vice versa.[15] The supernumerary parapodia regenerated between the grafted tegument and the body side of the worm present their dorsal surface in continuity with the dorsal side of the body side of the worm and vice versa. In other words, the supernumerary parapodia erase the tegument discontinuity brought by the grafting experiment, re-establishing a normal DV continuity. This situation mimics regeneration after parapodia ablation, where wound healing set up a tegument discontinuity. Interestingly supernumerary parapodia regenerated only when grafting was done close to parapodial nerves, a situation very close to limb regeneration in the newt. The necessity of having both DV discontinuity and nerves explains why parapodia regenerates only after deviation of nerves laterally close to the intersegment, a place without parapodial nerves where, normally, no parapodia can differentiate.[16]

Segment regeneration differs from parapodia regeneration because it depends on the production of brain hormones[17] and does not result from a tegument discontinuity caused by amputation. In contrast, it is driven by a gut extrusion so that wound healing operates from a

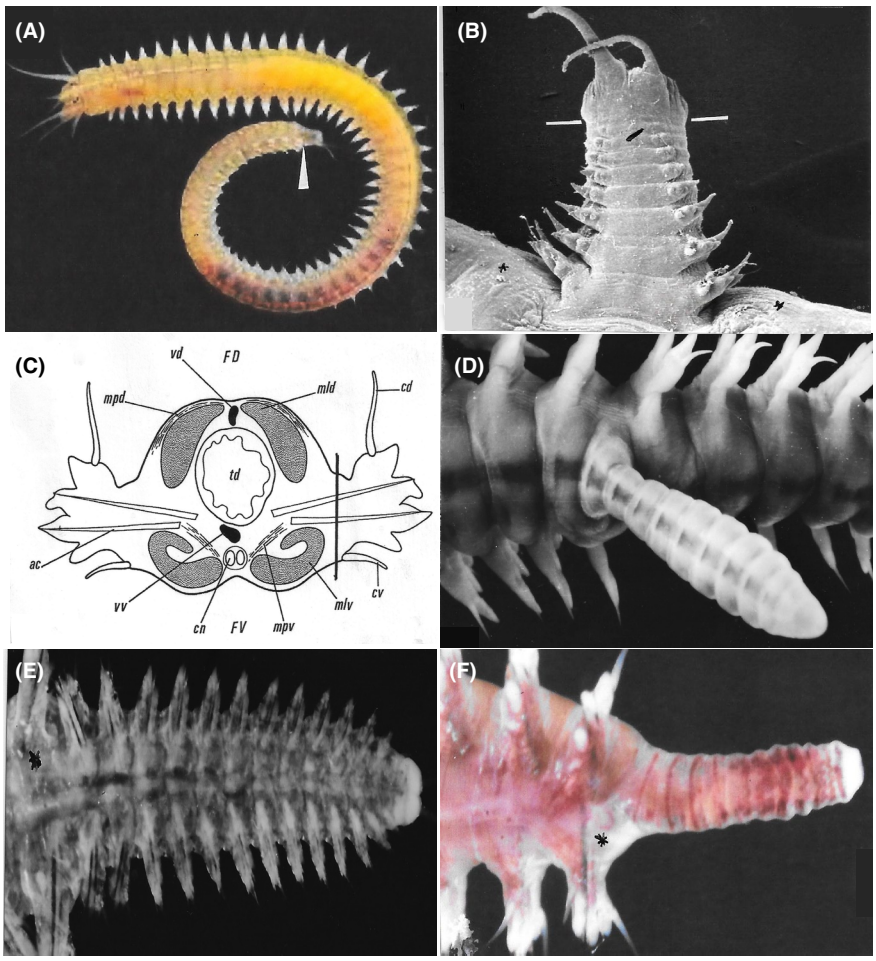

FIGURE 1 Nereid regeneration. A) General dorsal view of a live Nereis worm. The body is formed with a succession of setigerous segments bearing 2 parapodia per segment behind the head (left) until the last segment, the pygidium. In this case, the worm was accidentally amputated posteriorly (white arrow) and has already regenerated the pygidium and a clear area behind the stump corresponding to the proliferation and metamerization zone from which new setigerous segments are differentiating. The head, deprived of parapodia, is formed with 2 segments, the prostomium (with four eyes and two antennas) in front of the peristomium characterized by the absence of parapodia. Magnification: x0.4. **B)** Scanning electron micrograph of a young caudal regenerate 15 days postamputation (ventral view) showing clearly the postero-anterior differentiation of segments which can be appreciated at the level of segment length/width and parapodia length. The pygidium is well differentiated (2 anal cirri) and slightly larger than the base of the following segment differentiation zone. The differentiation of the new setigerous segments begins very close to the pygidium. The first morphological segment differentiation appears as small outgrows (black arrow) which progressively differentiate into parapodia; their presence allows to see that 8 setigerous segments are progressively differentiating from the pygidium to the stump. White lines: anterior limit of the pygidium; 2 asterisks: stump. Magnification: x10. **C)** Transversal section (FD, dorsal side; FV, ventral side) of a segment. D/V polarity is seen at the level of the pair of parapodia (lateral expansions) and of longitudinal muscles. Parapodia are composed of 2 parts each supported by a long acicula (ac) attached to the parapodial muscles (mpv for ventral parapodial muscle). The dorsal part is formed with a long dorsal cirrus (cd) and two-well separated lobes. The ventral part has the same composition, but the ventral cirrus (cv) is short and in general thinner than the dorsal one (cd); the 2 ventral lobes are always less separated than in the dorsal part. Bundles of setae (not drawn) spring up between the lobes of each part of the parapodia. Longitudinal muscles are present by pairs ventrally and dorsally: the ventral pair (mlv) presents a characteristic fold which does not exist on the dorsal pair (mld). All other structures are aligned in the sagittal plane: cn (nerve cord); td (gut); vv (ventral blood vessel); vd (dorsal blood vessel). Modified from Boilly et al 1975[31] and reproduced with permission. **D)** Dorsal regenerate growing on the middle of the dorsal side of the worm. The regenerate is well segmented, but segments are deprived of parapodia and the pygidium deprived of anal cirri. Magnification x5. **E)** Live specimen ventral view. Normal posterior regenerate following the last segment of the stump (larger than the 1st of the 12 regenerated segment) in the presence of the whitish nerve cord visible in the last segment of the stump and the first regenerated segments) around 20 days post amputation). The conical shape of the regenerate and the presence of lateral parapodia and of the unpigmented pygidium with its 2 anal cirri can be noted. Magnification x3. **F)** Aneurogenic posterior regenerate (without nerve cord) around 30 days post amputation. The absence of nerve cord in the 2 last segments of the stump, the cylindrical shape of the regenerate, the absence of parapodia on regenerated segments and of anal cirri on the pygidium can be noted. This regenerate is well metamerized as indicated by the presence of circular segmental blood vessel in each segment (around 10 regenerated segments). Magnification x5

junction between the tegument and the intestine wall. The role of this special type of wound healing was checked with experiments of gut deviation to the dorsal side of worms where normally no nerve cord exists; healing between these two tissues is followed by the regeneration of a segmented tail.[18] This regenerated tail, built only from the dorsal side of the worm presents a curious morphology and anatomy: all regenerated segments have the same size, giving a cylinder shape to the regenerate (Figure 1D), quite different from the conical shape in normal tail regeneration (Figure 1E). In addition, no parapodia differentiates on segments, no anal cirri appear at the extremity of pygidium and these regenerates differentiate no nerve cord. Interestingly segment regeneration depends on the presence of the endocrine action of the supra-oesophageal ganglion (generally called the brain) until the 3rd day postamputation.[19] However, it is not known if the inhibition of regeneration after brain removal results from an indirect action on regeneration, as the absence of the brain induces sexual maturation,[20] a high energy consuming phenomenon which could negatively affect regeneration.[21] However, the expression of Hox 3, normally expressed during posterior regeneration[22–24] was shown to be stimulated by methylfarnesoate (the putative brain hormone) in caudal body segment of brain deprived *Platynereis dumerilii*,[25] but in nereids it is not known if methylfarnesoate could restore segment regeneration after brain ablation and stimulate regeneration.

4 | THE ROLE OF THE NERVE CORD IN DV POLARITY OF REGENERATES

Segment regeneration without nerve cord induced on the dorsal side of the worm is also observed on amputated tail after deviation of the nerve cord from segments preceding amputation. In such a case, the regenerate (aneurogenic regenerates) (Figure 1F) is similar to those built on the dorsal side of worm after gut deviation.[26] These results clearly show that the nerve cord is not necessary for segment regrowth but plays a critical role in polarity of the regenerate. Experiments consisting in grafting tegument of aneurogenic regenerates on the dorsal or ventral side of normal worms showed that aneurogenic regenerates are deprived of DV polarity, all the tegument having a dorsal nature.[27] This situation explains some cases of parapodia neoformation, ventrally between the extremity of the stump and the anterior part of the regenerate, in presence of infiltrated nerve fibers.[28] The ventral nature is only expressed in the surrounding of the nerve cord[29] as a nerve cord grafted dorsally induces a polarity inversion of the dorsal side of the regenerate,[30] similar to what can occasionally be observed in wild regenerated nereids.[31] Interestingly, another family of polychaetes, the Sabellids, present a natural DV inversion (in the anterior part of the worm) which was shown to be linked to an inversion of the nerve cord position.[29] Therefore, in nereids the DV polarity is demonstrated by experimental results related to the control of parapodia regeneration. In planarians, it has been shown that the DV polarity corresponds to the expression of orthologs of Bone morphogenetic proteins (BMPs) and their signaling proteins SMAD.[32] Interestingly, in planarians, knockout of BMP orthologs ventralizes the dorsal side,[33–35] a situation similar to the result obtained after grafting a nerve cord on the dorsal side of nereids.[30] Conversely, knockout of a Noggin ortholog dorsalizes the ventral side of planarians,[36] a situation comparable to the aneurogenic regenerates obtained after removing the nerve cord. Therefore, the DV polarity is under the control of the nerve cord and that manipulating the nerve cord can reprogram this polarity during regeneration in nereids.

4.1 | Nerve cord and the DV polarity of the peristomium

All experiments and observations, reported above, that have highlighted the role of the nerve cord in the establishment of the DV polarity during regeneration concerned setigerous segments which exhibit a clear DV polarity. However, a particular segment, the peristomium, does not present this polarity. This segment, which appears in nereids to be fused with the prostomium to form the head is generally considered as formed by the fusion of the two first anterior metameres or of only the first metamere with the middle part of the trochophore. During the first stages of larva development, the peristomium differentiates parapodia like other segments; then these parapodia disappear leaving only what corresponds to dorsal and ventral cirri, which lengthen into 2 dorsal pairs of tentacular cirri.[37] The adult peristomium does not present a clear DV polarity (except for the mouth which opens ventrally). Moreover, its principal nerve tissue does not have a ventral position as in all other metameres; instead it runs vertically from the anterior extremity of the ventral nerve cord (sub-oesophageal ganglion) into the peristomium to the supra-oesophageal ganglion (brain), which is positioned dorsally in the prostomium and encircles the gut (circum oesophageal connectives).[38] As these circum oesophageal connectives correspond to the prolongation of the nerve cord in the peristomium, its influence on the polarity of this segment can be questioned as this segment has no parapodia. In fact, grafting experiments of the dorsal body side of the peristomium to the ventral side of this segment and vice-versa, or on a setigerous segment, never

induce parapodia.[39] Nevertheless, grafting peristomium body side on setigerous segment body side can induce (in 10% of cases) structures of cephalic type like antenna, tentacular cirri or jaws; more, this grafting experiment can also induce paropodia disappearance in some cases, a situation similar to what happens during development. These results, and the loss of parapodia during its early development, might be an indication of the absence of DV discontinuity in the peristomium. This could be in relation with the ventro-dorsal orientation of the nerves that come from the nerve cord. However, further investigations need to be done in order to appreciate more accurately the molecular differences between this particular segment and a normal setigerous segments.

4.2 | Nerve cord and the DV polarity of the pygidium

The pygidium is a particular structure originating from the posterior region of the trochophore larva and consequently characterized at first, as the prostomium, by the absence of coelom. During trochophore metamorphosis, corresponding to the differentiation of the first setigerous segments, the pygidium differentiates into a complex structure with the tissue existing in a metamere and particularly mesodermal structures (circular musculature), so that its cavity can be interpret as a coelom but deprived of the metameric metanephridia.[40] The pygidium does not bear parapodia but a pair of long anal cirri arising from its ventral extremity close to the anus. These anal cirri, which contain each a nerve connected with the extremity of the nerve cord, correspond to a marker of DV polarity as well the specific ventral muscles complex, probably in relation with the motility of the cirri.[40] The development of the anal cirri is nerve dependent, just like parapodia, as they do not differentiate in the pygidium of aneurogenic regenerates. However, ablation of the brain, which is known to inhibit segment regeneration has no effect on the pygidium which regenerates with its two anal cirri[41] (Figure 1B). Together, the regeneration of the pygidium is different from that of the other metameres and consequently independent from the SAZ. Another result supports this interpretation: X-Rays, which induce apoptosis of mesodermal cells of the SAZ, also completely stops the regeneration of the setigerous segments but not that of the pygidium.[42]

5 | THE ROLE OF THE NERVE CORD IN THE AP POLARITY

The nerve cord also appears to participate in the differentiation of the AP polarity in nereids, a role which was also proposed in another polychaete.[43] In nereids, all regenerated aneurogenic segments have the same size with the regenerate having a cylinder shape instead of a cone like the normal regenerate. That morphology may suggest that aneurogenic regenerates lack AP polarity. This idea led to amputate aneurogenic regenerates between segments; in these conditions, contrary to normal regenerates, only a pygidium without anal cirri can be regenerated but not the segments.[44] This experiment resulted in a lack of longitudinal discontinuity along the aneurogenic regenerate, as no discontinuity existed between the pygidium and the stump last segment of the amputated aneurogenic regenerate. In contrast, in amputated normal regenerates with a nerve cord, the amputation put the pygidium close to an already differentiated regenerated segment, a situation establishing a longitudinal discontinuity allowing the regeneration of new segments. These results show that only the AP discontinuity controls segment regeneration and that the nerve cord has no significant effect on cell proliferation in the SAZ since new segments continue to be produced in its absence, possibly because this activity is under the hormonal control of the brain. Nevertheless, we don't know if the action of the brain hormones on SAZ is mitogenic or if they just act as morphogens during regeneration; in this case, cell proliferation could be due to peripheral nerve fibers regenerated from the stump.[28] In planarians, Wnt was shown to establish the AP pattern along a gradient from the tail, but little is known in annelid regeneration. In the annelid *Platynereis dumerilii*, where several Wnt genes were reported[45] and expressed during posterior regeneration,[24] particularly in the nerve cord (Vervoort, personal communication), the canonic Wnt signaling pathway was shown to be involved in the proliferation/differentiation of neural cells.[46] Interestingly, Wnt is also expressed during regeneration of the spinal cord and axons after injury.[47,48] Moreover, Hox genes, expressed along the AP axis of planarians could also be involved in the control of the AP polarity during posterior regeneration of nereids.[22,23,49] In addition, fibroblast growth factors (FGFs) and heparin binding growth factors, which are known to be involved in cell proliferation during posterior regeneration in nereids[50,51] were recently shown to participate in axis elongation and patterning of the posterior regenerate in *Alitta (Nereis) virens*.[52] Interestingly, FGFs are also involved in AP interactions to induce limb regeneration in amphibians.[53] In these animals, heparan sulfate which acts as FGF coreceptors and FGF storage in the extracellular matrix, was shown to be associated to positional information.[54] These results obtained highlight the central role of FGFs in the control of regeneration and body polarities.

6 | CONCLUSION

Together, it appears that the nerve cord exerts an important function in nereid regeneration by creating a positional discontinuity in term of DV and AP polarity that is morphogenic after an amputation disrupting positional continuity. Nevertheless, this morphogenic capacity leads to a regeneration process for parapodia only if nerves are present and close to the amputation in order to stimulate cell proliferation, a situation similar to limb regeneration in amphibians. For segment regeneration, the nerve cord seems to regulate only the AP patterning. In nereids, the presence of the nerve cord is a prerequisite for regeneration by establishing a polarity pattern (DV for parapodia regeneration, AP for segment regeneration). Henceforth, the anatomical and experimental results described in this review now need to be translated in molecular terms to know both the biochemical nature of the factors involved and how they work together in the regeneration concert. We may then better understand the role of nerves in regeneration and potentially in other growth-related processes such as cancer.

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CONFLICT OF INTEREST

The authors have declared no conflict of interest.

AUTHOR CONTRIBUTIONS

B. Boilly, H. Hondermarck, and Y. Boilly-Marer contributed equally to the manuscript design and writing.

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