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Mechanisms controlling tissue assembly and morphogenesis in the developing embryo

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Uncovering the molecular mechanisms controlling tissue and organ formation represents a major challenge for future medicine. Our lab studies the molecular events leading to the generation of the contractile tissue, including muscles, tendons, and nerves in the Drosophila embryo as a model system to understand how tissues are being formed during embryonic development (Fig. 1). Previously we showed that a two-way communication between muscles and tendons is essential for the correct encounter of the two cell types, and their proper differentiation. While tendon precursors provide attraction cues for muscle migration, muscles are essential for the induction of tendon cell differentiation. Currently, our studies focus on three gene products, which are related to different aspects of that process:

The held out wing (how) gene encodes for two protein isoforms, How(S) and How(L), both of which are expressed by tendon and muscle cells. How(L) is expressed in pre-mature tendons and negatively regulates their terminal differentiation, while How(S) is highly expressed in mature tendons and positively regulates their differentiation. The How proteins are RNA-binding proteins that control the levels of their target mRNAs at the post-transcriptional level. This regulation is based on the opposing effects of How proteins on mRNA stability of their target mNRA. The key transcription factor controlling tendon cell differentiation, Stripe is a target mRNA of How. Therefore, in view of their opposing activities, the relative proportion between the repressor (How(L)) and the facilitator (How(S)) determines whether these cells remain at a premature state or will further differentiate. Our How-related research focuses on 3 topics: (1) the molecular basis of How activity, (2) the link between the establishment of muscle-tendon interactions and the relative proportion of How(L)/How(S), and (3) the identification of additional mRNA targets of How in other tissues.

The Vertebrates orthologue of the how gene is quaking, an essential gene for Schwann cell maturation and myelination. We are currently testing whether the different protein isoforms of Quaking (QKI-5, QKI-6 and QKI-7) regulate Schwann cell maturation in a similar manner to How in primary Schwann cells and in Drosophila glial and tendon cells. Preliminary data suggest that the QKI proteins regulate the levels of EGR2/Krox20, a key transcription factor in Schwann cell myelination, in opposing directions: QKI-5 represses, while QKI-6 and QKI-7 elevate EGR2/Krox20 levels. The similarity between maturation of Drosophila tendons and mammalian Schwann cells is summarized in Fig. 2.

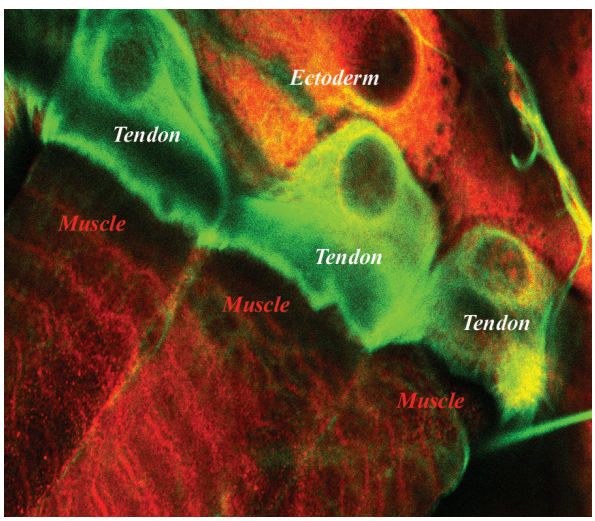

Fig. 1 *Muscles (red) and their specific tendons (green) in flat preparation of 3rd instar larvae.*

The kakapo gene product is essential for tendon cell maturation, neuronal extension, dendrites formation, and wing morphogenesis. Kakapo is a cytoskeletal linker protein, which associates with both the microfilament and microtubule systems. In mature tendons Kakapo is recruited to the cytoplasmic faces of the muscle-tendon junction and organizes a network of polarized microtubules, which is essential for muscle binding. The functional link between the unique Kakapo-based junction-associated cytoskeletal organization, and muscle-tendon binding as well as the identification of additional proteins in that complex are currently studied in the lab.

Vein is a Drosophila neuregulin-like differentiation factor, which among other functions forms the signal essential for tendon cell maturation. Vein protein is produced and secreted

by the muscle cell, and becomes localized at the muscle-tendon junction site where it activates the EGF receptor pathway in the tendon cell. Current analysis suggests that the Ig domain in Vein is essential for its localization at the muscle-tendon junction. Moreover, overexpression studies suggest that Vein lacking the Ig domain is hardly detected outside of the cells producing it in contrast to the intact Vein. The possibilities that Vein lacking the Ig domain is not secreted normally, or that it is rapidly degraded following secretion, are currently addressed in the lab.

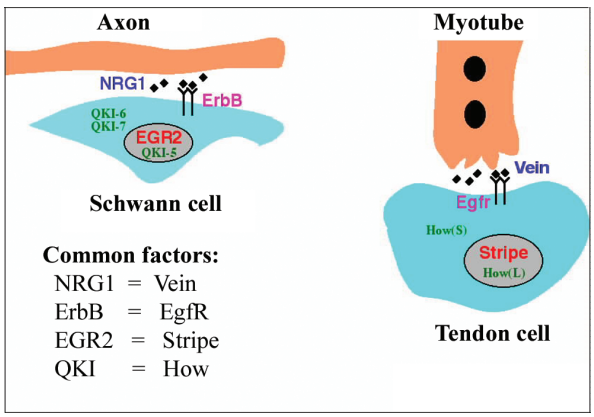

Fig. 2 *Similar mechanisms control tendon and Schwann cells maturation. How(L)/QKI-5 maintain the cell at a pre-mature differentiation state. Cell maturation is induced by Vein/NRG1 and How(S)/QKI-6,QKI-7.*

Selected Publications

Becker, S., Pasca, G., Strumpf, D., Min, L., and Volk, T. (1997) Reciprocal signaling between Drosophila epidermal muscle attachment cells and their corresponding muscles. Development 124, 2615-2622.

Yarnitzky, T., Min, L., and Volk, T. (1997) The Drosophila neuregulin-homologue, Vein, mediates inductive interactions between myotubes and their epidermal attachment cells. Genes & Dev. 11, 2691-2700.

Yarnitzky, T., Min, L., and Volk, T. (1998) An interplay between two EGF-receptor ligands, Vein and Spitz, is required for the formation of a subset of muscle precursors in Drosophila. Mech. Dev. 79, 73-82.

Strumpf, D., and Volk, T (1998) Kakapo, a novel cytoskeletal-associated protein is essential for the restricted localization of the neuregulin-like factor, Vein, at the muscle-tendon junction site. J. Cell Biol. 143, 1259-1270.

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Volk, T. (1999) Singling out Drosophila tendon cells: a dialogue between two distinct cell types. Trends Genet. 15, 448-453.

H. Nabel-Rosen, G. Volohonsky, A. Reuveny, R. Zaidel-Bar, and T. Volk. Two isoforms of the Drosophila RNA-binding protein, How, act in opposing directions to regulate tendon cell differentiation. Dev. Cell (in press).

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