1 INTRODUCTION

Sensing the environment and responding or adapting is key to an organism's survival. Organisms sense the environment by detecting physical and chemical stimuli, such as light, temperature, pressure, gravity, sound, chemicals, pH, osmolarity, etc., This can be observed from prokaryotes to eukaryotes and the complexity of sensory system increases up the evolutionary tree. Out of all the sensory systems, mechanosensation may be the most primitive because the deforming stimuli can be generated from thermal molecular agitation to osmotic pressure gradients, which can harm the plasma membrane. Mechanosensation is ubiquitous and in prokaryotes the sensor and effector molecules are one and the same molecule (Anishkin and Kung, 2005). Where as in higher organisms different mechanical stimuli are detected by different receptors and integration schemes thus eliciting an array of homeostatic reflexes and behaviors (Hamill and Martinac, 2001).

1.1 Prokaryotic molecules of mechanosensation

Prokaryotes, had to cope with the turgor created by the extra and intracellular osmolarity change in different environments, which could lead to cell lysis. As the cell wall could protect only to an extent, mechanosensory channels (Msc) which can be opened by membrane stretch seem to play an important role in the protection of cells during sudden osmotic change before other transcriptionally controlled slower protective mechanisms are activated (Kung C., 2005). It has been shown that many bacterial channels have mammalian channel homologues (Table 1, Booth, et al., 2003) and models obtained from the crystal structures of these have led us to predict the mechanism of action of different channels.

As the basis of selectivity and gating in ion channels evolved early in the history of life on earth and has been deployed by bacteria for millions of years (Booth, et al., 2003). The same mechanism of opening proposed for some of the bacterial channels may be true for at least some of the respective mammalian mechanosensitive channels. The mechanosensitive channels in bacteria are summarized in table 2 with their ion selectivity (Edwards, et al., 2004).

Ion specificity	Type of channel	Bacterial example
K^+	Anionic	KcsA
	Voltage-gated	KvAP
	Inward Rectifier	KirBac1.1
	Ligand-gated	MthK, GluR0, Kch
	Other**	
Na^+	Voltage-gated	NaChBac
Cl^-	Voltage-gated	CICA, CICB
	Bestrophin related	YneE
Other	Glutathione-gated K^+ efflux	KefC
	K^+ uptake proteins	KtrB, KdpA

Table 1. Bacterial homologues (known crystal structure) of mammalian ion specific channels

**There are many K^+channel homologues related to KcsA that possess additional amino terminal or carboxy terminal domains that are not similar to the four crystallized examples. (Adapted and modified from Booth, et al., 2003)

Channel	Ionic preference		Distribution
MscL		None	Bacteria and some fungi
MscS	MscS	Anions	Bacteria, archaea, *S. pombe*, *Arabidopsis*.
	MscMJ	Cations	
	MscMJLR	Cations	
MscK		none	γ-proteobacteria
MscM*		Not determined	Not determined

Table 2. Mechanosensitive ion channel in bacteria their ion selectivity and distribution
*The gene(s) encoding MscM has not been identified
(Adapted and modified from Edward, et al., 2004)

1.2 Mechanosensation in Coenorhabditis elegans.

Different behaviors are exhibited by *C. elegans* in response to different mechanosensory input. About 10% of the all neurons are involved in sensing touch (O'Hagan and Chalfie, 2006) and the molecules which could be responsible can be grouped into ion channel like degenerins, membrane bound associated proteins, extra cellular matrix proteins and cytoskeletal proteins (Fig. 01), unlike the simple scheme present in prokaryotes.

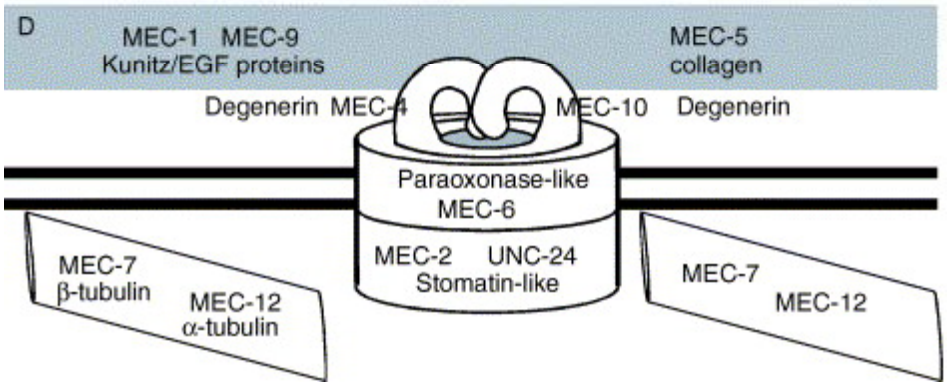

Fig.01. Proteins needed for mechanosensation in touch receptor neurons in *C.elegans*. Adapted and modified from O'Hagan and Chalfie, (2006).

1.2.1 Genes directly involved in mechanosensation

Mec4 and Mec10 are members of the Degenerin family, which are members of DEG/EnaC (degenerin/epithelial Na^+ channel) superfamily of proteins (Fig.02). They have intracellular N-and C-termini, two transmembrane (TM) domains and a large extracellular cysteine rich domain (Reviewed by O'Hagan and Chalfie, 2006). Different experiments have shown that TM II is likely to form the pore forming domain. They are reported to form heteromeric channels. (Reviewed by O'Hagan and Chalfie, 2006)

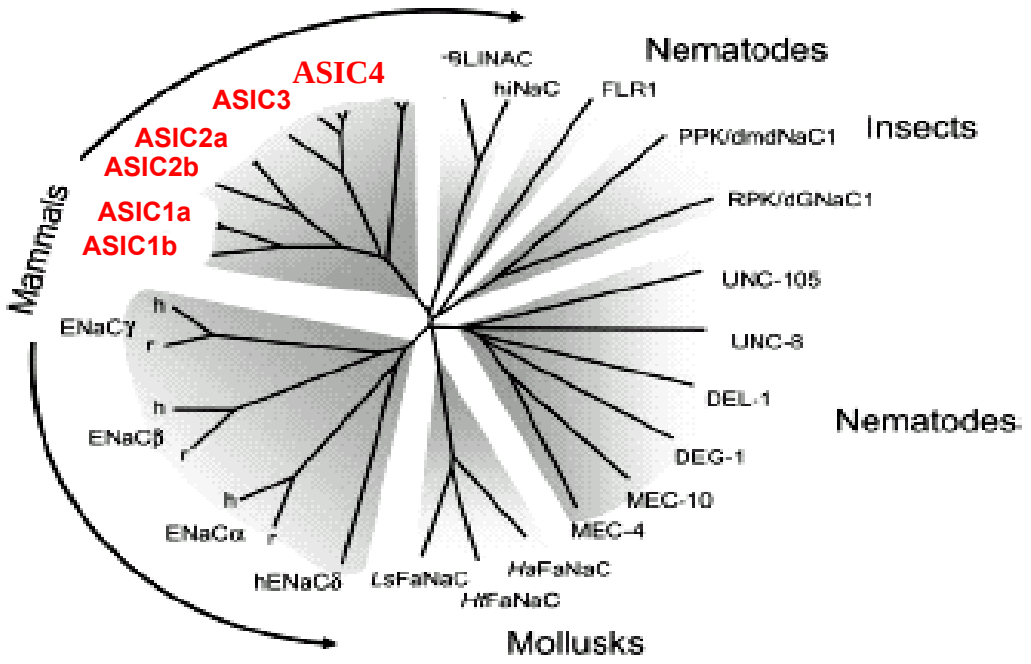

Fig.02. Relationship of MEC-4 and MEC-10 with respect to other DEG/ENa^+C family members. (Adapted and modified from Kellenberger and Schild, 2002)

Second category of proteins are membrane associated MEC-2 a stomatin like protein, MEC-6 a paraoxonase like protein and UNC-24 a protein with a stomatin domain as well as a lipid transfer domain. MEC-2 is an intracellular protein anchored to the inner plasma membrane. Many reports have shown that MEC-2 interacts with the stomatin domain with the MEC-4/MEC-10 and the C-terminal interacts with other proteins. It is reported that *unc-24* mutations enhances temperature sensitive alleles of *mec-4* and *mec-6* (Zhang, et al., 2004).

Extra cellular matrix (ECM) proteins are MEC-1, MEC-5 and MEC-9. Mutations in these cause touch insensitivity. MEC-1 and MEC-9 encodes proteins with multiple EGF and Kunitz domains where as MEC-5 is a collagen like molecule with out any similarity to other collagens except for the Gly-X-Y repeat. Though the function of MEC-1 seems to be for the attachment of the touch neuron to the body wall, C-terminal seems to be more important for the touch sensitiveness irrespective of the attachment of the neuron. Though MEC-1, MEC-5 and MEC-9 are reported to be positioning the MEC-4, other channel functions like interacting with the mature channel complex seems to be more important.

Microtubule proteins are MEC-12 α-tubulin and MEC-7 ß-tubulins, which form 15-protofilament microtubule bundles. The roles of these proteins are not yet known as the mutations cause behavioral insensitivity to touch but mechanoreceptor currents (MRC) are intact in the mutant.

1.2.2 Genes needed for differentiation

Different genes like UNC-86 and MEC-3 transcription factors are needed for the differentiation of touch receptor neurons. UNC-86 is required for the differentiation of neuroblast precursors into touch receptor neurons. UNC-86 initiates MEC-3 transcription, which determines the final fate of the cells. In addition to these transcription factors, MEC-8, which is a MEC-2 RNA processing protein is also important may be because it is needed for other as yet unidentified mechanotransduction proteins in addition to MEC-2.

1.3 Mechanosensory neurons in vertebrates:

Mechanosensory neurons are diverse in their functional and receptive properties. They can be divided as Aß fibers, which are thickly myelinated, have fast conduction velocities (>10 m/s). Thinly myelinated Aδ fibers have slower conduction velocities (<1 up to 10 m/s). Sparsely

myelinated c-fibers conduct slowly (<1 m/s) (Koltzenburg, 1997, Djouhri, and Lawson, 2004). Aß fibers are generally large, Aδ fibers are medium sized and c-fibers are small sized neurons. By their adaptation properties, Aß can be further classified as rapidly adapting (RA) or slowly adapting (SA) mechanoreceptors. Aδ can be classified as D-hairs and AM fibers. RA, SA and D-hairs are low threshold mechanoreceptors (Fig. 03). At the molecular level, expression of different molecules both intracellular and extracellular might be influencing the functional properties of these neurons (Price, et al., 2000, Fang, et al., 2002, Shin, et al., 2003, Ichikawa, et al., 2001).

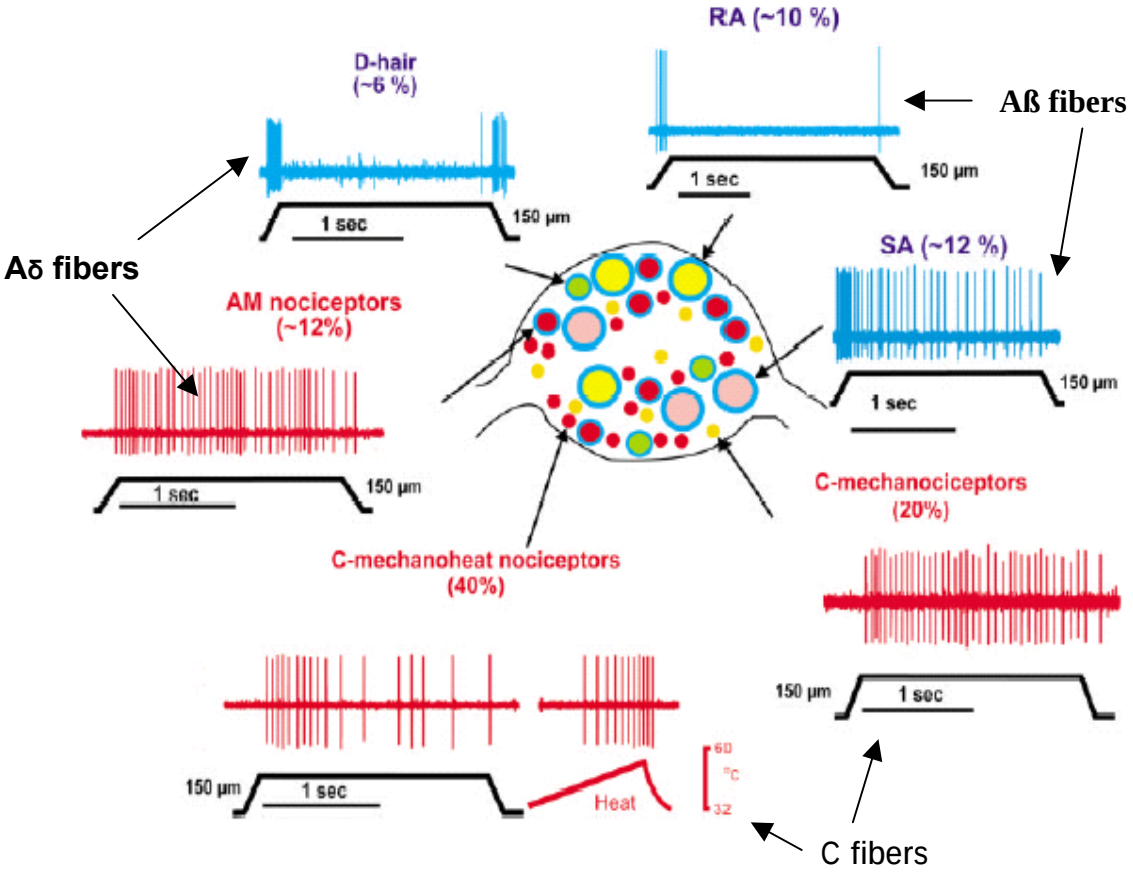

Fig.03. Different sensory fibers innervating skin and their functional characteristics

Neurotrophins (NT) play an important role in the development, differentiation and (or) survival of DRG sensory neurons. (Carroll, et al., 1998, Ernfors, et al., 1994, Stucky, et al., 2002, Lewin and Badre, 1996, Pezet and McMahon, 2006). At birth 70-75% neurons are responsive to NGF and later on these neurons differentiate to other subtypes resulting in different characteristics reflected in the expression of different ion channels, neuropeptides and so on (Reviewed in Pezet and McMahon, 2006) differentially. They act through Trk receptors and p75 to affect its functions (Fig. 04) in both autocrine and paracrine fashion (Acheson, and Lindsay1996).

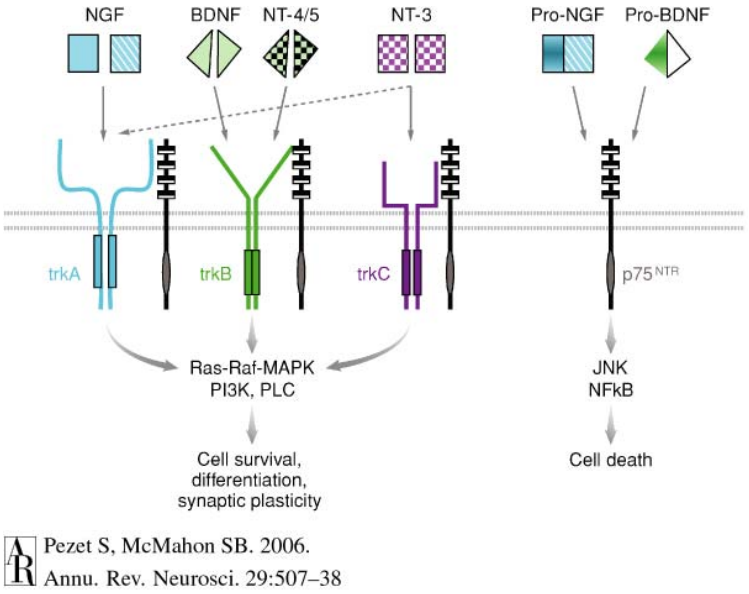

Fig. 04. Neurotrophic factors and their receptors

1.4 Identification of DRG specific genes

There are reports in which DRG cell specific genes were isolated from a subtracted library (Akopian and Wood, 1995, Akopian, et al., 1996) subtractive hybridization that were not cross reacting with liver, kidney, heart, spleen, cerebellum, and cerebral cortex. By sequence analysis it was shown that both known and novel identifiable transcripts were present in those screens.