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Review

C. elegans DAF-12, Nuclear Hormone Receptors and human longevity and disease at old age

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Abstract

In *Caenorhabditis elegans*, DAF-12 appears to be a decisive checkpoint for many life history traits including longevity. The daf-12 gene encodes a Nuclear Hormone Receptor (NHR) and is member of a superfamily that is abundantly represented throughout the animal kingdom, including humans. It is,

Abbreviations: AR, Androgen Receptor; BLAST, Basic Local Alignment Search Tool; CAR, Constitutive Androstane Receptor; CETP, Cholesterol Ester Transfer Protein; COUP-TF1/COUP-TF2, Chicken Ovalbumin Upstream Promoter Transcription Factor 1/2; CYP7A1, cholesterol-7-alpha-hydroxylase; DAF, Dauer Formation Influencing Genes; DAX1, DSS-AHC critical region on the X chromosome; DBD, DNA-binding domain; EAR1A/EAR1B/EAR2, ERBA related 1 A/B/2; ERA/ERB, Estrogen Receptor Alpha/Beta; ERRA/ERRB/ERRG, Estrogen Related Receptor Alpha/Beta/Gamma; FXR, Farnesoid X Receptor; GCNF1, Germ Cell Nuclear Factor; GR, glucocorticoid receptor; HNF4A/HNF4G, Hepatocyte Nuclear Factor 4 A/G; IGF-1R, Insulin-Like Growth Factor 1 Receptor; IR, Insulin Receptor; LBD, ligand binding domain; LRH1, Liver Receptor Homologue; LXRA/LXRB, Liver X Receptor Alpha/Beta; MR, Mineralocorticoid Receptor; NGFIB, Nerve Growth Factor-Induced Clone B; NHR, Nuclear Hormone Receptor; NOR, Neuron Derived Orphan Receptor; NOT, Nuclear Receptor of T-cells; PNR, Putative Neurotransmitter Receptor; PPARA/PPARG/PPARD, Peroxisome Proliferator Activated Receptor Alpha/Gamma/Delta; PR, Progesterone Receptor; PXR, Pregnane X Receptor; RARA/RARB/RARG, Retinoid Acid Receptor Alpha/Beta/Gamma; RORA, RAR Related Orphan Receptor Alpha; ROS, reactive oxygen species; RXRA/RARB/RARG, Retinoid X Receptor Alpha/Beta/Gamma; SF1, Steroigenic Factor 1; SHP, Small Heterodimer Partner; SNP, single nucleotide polymorphism; THRA/THRB, Thyroid Hormone Receptor Alpha/Beta; TLX, Tailless; TR2/TR4, Testicular Orphan Receptor 2/4; VDR, Vitamin D Receptor

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however, unclear which of the human receptor representatives are most similar to DAF-12, and what their role is in determining human longevity and disease at old age.

Using a sequence similarity search, we identified human NHRs similar to *C. elegans* DAF-12 and found that, based on sequence similarity, Liver X Receptor A and B are most similar to *C. elegans* DAF-12, followed by the Pregnane X Receptor, Vitamin D Receptor, Constitutive Andosteron Receptor and the Farnesoid X Receptor. Their biological functions include, amongst others, detoxification and immunomodulation. Both are processes that are involved in protecting the body from harmful environmental influences. Furthermore, the DAF-12 signalling systems seem to be functionally conserved and all six human NHRs have cholesterol derived compounds as their ligands.

We conclude that the DAF-12 signalling system seems to be evolutionary conserved and that NHRs in man are critical for body homeostasis and survival. Genomic variations in these NHRs or their target genes are prime candidates for the regulation of human lifespan and disease at old age.

Keywords: DAF-12; Nuclear Hormone Receptors; Longevity; Lipid metabolism; Detoxification

1. Introduction

The nematode worm *Caenorhabditis elegans* is a valuable experimental model for research into ageing, because its lifespan is influenced by signalling systems that are well characterised and highly conserved throughout evolution. In *C. elegans*, environmental conditions, such as food availability, temperature and population density, are monitored by sensory systems. To prevent damage and to maintain homeostasis the individual worm constantly has to adjust itself to its changing environment through alterations in essential traits, such as metabolic rate, developmental time and reproduction. Under favourable conditions, *C. elegans* develops through four larval stages and two adult stages. Under unfavourable conditions, *C. elegans* turns into an alternative highly resistant diapausal dauer larva. During this optional life stage, all major life history events (development, growth, metabolic rate and reproduction) are slowed down and although the worm is capable of movement, it is mainly inactive and non-feeding. When conditions turn favourable again, the larva resumes its normal developmental program to an adult, without loss of post-dauer lifespan, adding up to 60 days to the normal maximum lifespan of 15 days from egg to adult (Klass and Hirsh, 1976). This suggests that during the dauer state the worm does not age. Many genes in the worm's signalling systems influence dauer formation and are therefore called *daf* genes. Mutations in these genes can prolong the lifespan of the worm by favouring dauer formation. Strikingly, some of these mutations also extend adult lifespan up to three-fold (Gems et al., 1998), indicating that these mutations also influence the rate of ageing in the adult worm.

Since the worm's signalling systems are also present in other species, and are therefore believed to be functionally conserved, their role in longevity in other species is subject of intense research. The genetic mutations extending lifespan in the worm also extend lifespan in *D. melanogaster* and mice. For example, it was first discovered that the *C. elegans daf-2* mutant was longlived (Kenyon et al., 1993). Later, it was discovered that the *daf-2* gene shows homology to the mammalian genes encoding the Insulin Receptor (IR) and Insulin-Like Growth Factor 1 Receptor (IGF-1R) (Kimura et al., 1997), which are