

# Morphologic characteristics of the human ciliary muscle

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## Abstract

The present review focusses on the morphological characteristics of the normal human ciliary muscle. It develops in the second and third trimester during pregnancy but continues to change after birth with developing accommodation. The mature muscle forms three distinguishable portions which are connected but show individual characteristics. The outer portion originates and inserts with tendon-like structures, while the inner portion forms a sphincter-like appearance. The distinct different innervation is not yet completely described, nor exist portion-dependent summaries of the cytological characteristics. The specific intracellular, membranous, and extracellular components described in the literature are listed and supplemented with own observations.

## Dedication

This review is dedicated to my scientific instructors Prof. Johannes W. Rohen and Prof. Elke Lütjen-Drecoll

## Introduction

Accommodation is one of the crucial conditions for foveal vision. The active change of the lens curvature is induced by the ciliary muscle, its counterpart are passive forces like the elasticity of the lens itself and of Bruch's membrane. In the present review the specifics of this muscle in the human are highlighted to better understand its unique role in the concert of uveal smooth muscle cells. Since there are known differences in the morphology and function of the ciliary muscle in different species, only data from investigations using human tissue or human cell cultures were included.

The step-wise discovery of the human ciliary muscle in the early 19<sup>th</sup> century was only described recently [1] and is not part of this review.

## Three-dimensional architecture

### Development

The early development of the ciliary muscle was first described by Herzog [2] and Seefelder & Wolfrum [3] using light microscopy of fetal human eyes; extended views were described in ophthalmic text books [4,5] and a first electron-microscopic analysis was performed by Sellheyer and Spitznas [6]. According to this literature, differentiation of the human ciliary muscle starts around week 12 forming at first the outer portion (meridional portion or Brücke's muscle). The inner portion (circular portion or Müller's muscle) shows first characteristic arrangements at week 14, the intermediate portion (radial/ reticular portion or Iwanoff's muscle) develops successively. The muscle cells and the interwoven fibroblasts derive from a common mesenchymal cell. Population present from week 10 on. Muscle cell differentiation continues up to week 16, followed by continuing maturation. First axons demonstrating an innervation of the smooth muscle cells were described in week 15. A detailed description of the development of human ciliary muscle innervation remains to be determined.

At birth, the human ciliary muscle appears still somewhat immature [7-9] and develops in the first year of life to its mature appearance. Although the different muscle portions act as one unit,

distinct exposures lead to local thickness shifts in children eyes: accommodative work load stimulates the anterior (inner) part of the ciliary muscle, while the posterior (outer) part is more affected in myopic conditions [10].

### Mature appearance

The mature human ciliary muscle contains of three main portions which are present in the whole circumference of the eye showing no quadrant differences. The smooth muscle cells of the outer portion are arranged from posterior to anterior (meridional), forming clear origin and insertion zones. At the posterior attachment (origin) of the outer portion, the muscle cells are mainly connected to the elastic fibers of the choroidal stroma [11-14]. The smooth muscle cells form an irregular, slender line and develop a star-like appearance [15]. The anterior attachment (insertion) of the outer portion is partly at the scleral spur, which develops early during maturation [16], and partly at the corneo-scleral portion of the trabecular meshwork [17-20]. They are attached to a special fibrous-elastic tissue which continues with elastic components of the trabecular meshwork and the scleral spur [21-23].

The smooth muscle cells of the inner portion have a circular orientation. They form bundles separated by small connective tissue sheaths. It was mentioned that it is more pronounced in the nasal quadrant [13] but a great interindividual variation could not confirm this observation. The bundles of muscle cells show some contact to the intermediate portion which connects the two main portions together and shows therefore a reticular appearance of the smooth muscle cells. A detailed description of the inner bundle arrangement of the human ciliary muscle has up to now not been published.

### Changes with age

Numerous cross-sectional studies of age-related changes of the human ciliary muscle focused on its postmortal morphology and described a decrease of smooth muscle cells in combination with an

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**Key words:** ciliary muscle, development, ageing, innervation, cytology

**Received:** June 03, 2017; **Accepted:** June 27, 2017; **Published:** June 30, 2017

increase of connective tissue. The outer portion of the ciliary muscle thereby decreased in area and length with age, while the area of the inner portion increased, adopting an anterior-inward position of the whole muscle [7,8,16,24-29]. The role of the intermediate portion of the ciliary muscle is discussed controversially in this literature. In vivo cross-sectional measurements using MRI [30-32], sonography [33-36], or OCT [37,38] confirmed the age-related increase in ciliary muscle area thickness without alteration of the inducible ciliary muscle activity. Findings of the ciliary ring diameter were controversially – the anterior-inward position depended mainly on the state of the lens rather than the muscle itself.

## Innervation pattern

Cholinergic nerve fibers are abundant in all parts of the human ciliary muscle. They form a dense neuronal network around and within the muscle fiber bundles and to a great amount do not co-localize with other specific neuronal markers like bNOS, VIP or galanin. Intense acetylcholin esterase presence was described in the anterior part of the ciliary muscle [39]; own staining using an antibody against VACHT confirmed the dense innervation throughout the muscle. Only sparse VIP immunoreactive nerve fibers exist in the ciliary muscle [40]; single nerve fibers with the typical varicose appearance were present within all portions and all regions. They probably do not supply the muscle itself [41].

Intrinsic neurons are known to exist in the human ciliary muscle since the first description by Müller 1859. They have been confirmed subsequently, the most recent characterization dating from 1995 [42,43]. Their location is restricted to the inner parts of the ciliary muscle, their presence is restricted to species with high requirements for visual acuity. All neurons were NOS positive and TH/NPY/VIP negative. The somata of the neurons receive CGRP and SP positive nerve endings.

Adrenergic nerve fibers are present in the ciliary muscle, but to a much lower degree than the cholinergic nerve fibers. They have been hypothesized as early as 1891 from experiments on dogs [44] but controversially discussed thereafter. Using a fluorescence technique, the nerve fibers could be demonstrated in the human ciliary muscle [45]. Associated peptides to adrenergic nerve fibers included neuropeptide Y [46] and dopamine-beta-hydroxylase [47]. Clinical investigations confirmed the minor role of these nerves in ciliary muscle function [48,49] and pronounced interindividual differences [50]. Own unpublished observations revealed only few VMAT-2 positive nerve fibers within the ciliary muscle, but no fibers containing NPY.

Substance P positive nerve fibers in the ciliary body were only described around blood vessels [51,52]. In contrast, Substance P was identified as a specific motor excitatory transmitter in isolated human ciliary muscle cells [53].

Sensoric (proprioceptive) nerve fibers are described in the scleral spur of human eyes representing tendon-like sensors of the outer ciliary muscle portion [54,55] and in the connective tissue around the inner muscle portion [15]. Their connection to the neurons marked with calcitonin gene related peptide [56,57] is not fully proven.

## Cytological characteristics

### Intracellular components

All human ciliary muscle cells show typical characteristic of smooth muscle cells: they stain with antibodies against alpha smooth muscle

actin [20,58-61], vimentin [58,59,61], desmin [58-61], smooth muscle myosin (polyclonal antibody, no further specification so far [19]), and calponin [62]. There is no literature about the presence of calmodulin and tropomyosin in the ciliary muscle; own unpublished investigations showed that the human ciliary muscle cells do not contain caldesmon (in contrast to the description of calponin and caldesmon in the mouse ciliary muscle cells [63]).

The human ciliary muscle contains some other identified proteins: the myosin-like protein myocillin [64], the small heatshock protein alphaB-crystallin [65,66], optineurin [60], fibroleukin [60], and galanin [67]. A novel splicing variant of the regulator of G-protein signaling 5 (RGS5) was also described for the human ciliary muscle cells [68]. Some histochemical differences between the different portions of the ciliary muscle were noted earlier [69].

### Membrane elements and receptors

Numerous investigations focused on the detailed interaction between the nerve fibers and the ciliary muscle cells:

After general evidence for muscarinic receptors [70,71], numerous work focused only on the subtype m3 [71-75], although the subtypes m1 and m2 were also detected [76]. A first localization study revealed that the muscarinic receptor subtypes m2 and m3 were predominantly in the inner portion, m5 predominantly in the outer portion of the ciliary muscle [77]; small amounts of the subtypes m1 and m4 were mentioned, and the presence of all subtypes m1-m5 with a dominance of m3 were confirmed [78].

The general presence of adrenergic binding sites [79] was specified to mainly beta2-adrenoceptors [70,80,81], but also beta1-adrenoceptors [81] and alpha2-receptors [82,83]. A localization study showed the ubiquitous presence of beta2- and alpha1-adrenoceptors in the inner and outer portion of the ciliary muscle [84].

Additional receptors related to potential neurotransmitters and reported to be present in the human ciliary muscle include the serotonin-2 receptor [85], the cannabinoid CB1-receptor [86,87], and the galanin-receptors galR3 (ubiquitous present in the ciliary muscle) and galR1 (restricted to the inner rim of the ciliary muscle) [88].

Prostaglandin binding sites [89] are of great interest due to therapeutic application of prostaglandins. From the E-receptors, EP1 is present all over the ciliary muscle [90-92]; EP2 [93-96] and EP4 [94,96] could also be demonstrated to be present. A detailed morphologic demonstration included all four E-receptors [97]. The prostaglandin receptor FP could also be identified [60,87,90,94,98-101]; however, it is located mainly in the inner portion of the ciliary muscle [91,92,97]. Beside these two groups, the TP receptor [90] and the DP receptor [93,95,102,103] were described for the human ciliary muscle; IP receptors were not mentioned.

After a first description of functional endothelin receptors in human ciliary muscle cells [104], the endothelin receptor A was identified [105-107], and less prominent also the endothelin receptor B [107].

Further membrane proteins described to be present in the human ciliary muscle include syndecan 1-4 [108], angiotensin receptor [70], aquaporin 1 [60], bradykinin B1 and B2 receptors [109], bradykinin B2 receptor [110], Somatostatin-receptor 1 and 2 [111], Insulin-receptor [112], type B natriuretic peptide receptor [113], and histamine 1 receptor [114].

A prominent characteristic of all human ciliary muscle cells is the lack of gap-junctions [115] identifying this muscle as a multiunit type of smooth muscle. Functional investigations of cultured ciliary muscle cells revealed a typical smooth-muscle like behavior [116,117].

### Extracellular components

The extracellular environment around the single ciliary muscle cells is mainly investigated regarding its matrix proteins and related enzymes.

The main collagens include collagen type I and type III [118-120], type IV [118-121], type VI [120-122], and collagen type XIII [123]. While most collagens showed an even distribution within the ciliary muscle, collagen type VI was only sparse within the muscle bundles and more dominant in the outer portion towards the sclera. Additional demonstrated extracellular matrix proteins in the human ciliary muscle include fibronectin and laminin [118,120,121]; own unpublished observations showed a dense network of fibrillin and fibronectin, but only single fine vitronectin fibrils around human ciliary muscle cells.

Elastic fibers are present in the connective tissue between the muscle bundles. Staining with antibodies against elastin showed a fine network of fibers pronounced in the more anterior part of the outer portion (own unpublished observations).

Human ciliary muscle cells produce a number of enzymes including metalloproteinases [120,124-126], its tissue inhibitors TIMP-1 and TIMP-2 [127], and tissue transglutaminase (own unpublished observations). Further identified factors are IGF-1 [60], promelanosome-concentrating hormone [60], TRAIL [60], Endothelin-1 [107], kallikrein and kininogen [109], and connective tissue growth factor [128].

In connection with the prostaglandin receptor described above, some information exists about the local release of arachidonic acid and prostaglandins in cultured human ciliary muscle cells [129,130].

### Conclusion

Combining the described morphological characteristics, the human ciliary muscle appears as a highly specific smooth muscle with some unique characteristics. These include the three-dimensional structure of the muscle as a whole forming a mainly complete sphincter with its inner portion, the distinguishable function of different portions of the muscle, and the tendon-like attachment of the outer portion at the choroid and the scleral spur/ trabecular meshwork.

Some aspects of its morphology are already well characterized, while a more systematic investigation of the muscle is still missing. This might be caused by its specific role for accommodation and aqueous humor outflow regulation, and the focused research performed in these two respects.

Fortunately, this review stimulates some researchers to more precisely describe the normal appearance and characteristic of this exceptional muscle in the human eye, especially its three-dimensional appearance within the circumference and its multiple innervations. This might help to better understand its detailed functions, and to further discuss pathological changes and conditions involving the ciliary muscle such as presbyopia and glaucoma.

### Conflict of interest

There are no conflicts of interest.

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