Primary cilium - antenna-like structure on the surface of most mammalian cell types

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Abstract. The primary cilium is a sensory solitary non-motile microtubule-based organelle protruding in the quiescent phase of the cell cycle from the surface of the majority of human cells, including embryonic cells, stem cells and stromal cells of malignant tumors. The presence of a primary cilium on the surface of a cell is transient, limited to the quiescent G₀ phase and the beginning of the S phase of the cell cycle. The primary cilium is formed from the mother centriole. Primary cilia are key coordinators of signaling pathways during development and tissue homeostasis and, when defective, they are a major cause of human diseases and developmental disorders, now commonly referred to as ciliopathies. Most cancer cells do not possess a primary cilium. The loss of the primary cilium is a regular feature of neoplastic transformation in the majority of solid tumors. The primary cilium could serve as a tumor suppressor organelle. The aim of this paper was to provide a review of the current knowledge of the primary cilium.

Introduction
The primary cilium was discovered in the nineteenth century. Over one hundred and forty years passed between the discovery of this organelle and a deep appreciation of its important functions. It is a solitary sensory non-motile microtubule-based organelle protruding in the quiescent phase of the cell cycle from the surface of the majority of human cells, including embryonic cells, stem cells and stromal cells of malignant tumours, with the exception, for example, hepatocytes and haematopoetic cells. The primary cilium acts as a cellular antenna that senses extracellular signals from the environment and translates them into specific intracellular signalling cascades [1]. The primary cilium consists of an axoneme with nine peripheral microtubule doublets arranged around a central core lacking two central microtubules: the 9 + 0 pattern (contrary to motile cilia with the 9 + 2 pattern), surrounded by the ciliary membrane, which is a specialized domain extension of the cell membrane. The axoneme extends from the basal body, which is derived from the mother centriole of the centrosome [2]. The cilia do not contain ribosomes. Proteins are not synthesized within the cilium. Therefore all proteins required to build and maintain the cilium, as well as the signalling proteins
required for cilia functioning, are synthesized in the cell body and transported into and out of the cilium [3]. This bidirectional microtubule-based transport is known as intraflagellar transport [4].

The term “primary cilium” was first applied by Sorokin for airway epithelial cells, which start out with a single cilium, thus called “primary”, and then, during differentiation, form large numbers of additional motile cilia, which are called “secondary” cilia [5, 6]. Most cells of the body have just a single cilium and, by analogy with the single initial cilium of the airway cells, these single cilia are now generally called primary cilia. The primary cilium is essential for the orientation of the cytoskeleton in the cell and the orientation of the cell in the tissue. The main difference between primary and secondary cilia is in centriologenesis. Basal bodies/centrioles of secondary cilia are not formed by the duplication of pre-existing centrioles (as primary cilia), but are formed on the surface of spherical precursor structures called deuterosomes, which originate de novo in the cytoplasm from fibrogranular material.

The lengths of primary cilia are more variable than the length of motile cilia. It was observed that primary cilia in the rat liver are approximately twice as long in the large bile ducts (7.35±1.32 μm in length) than in the small bile ducts (3.58±1.12 μm in length) [7]. Primary cilia elongate under unfavourable conditions, such as during hypoxia or starvation.

Relationship between the primary cilium cycle and the cell cycle
Primary cilia exhibit dynamic patterns of assembly and disassembly as they progress through the cell cycle [Scheme 1]. Centrosomes, which are composed of two centrioles arranged perpendicularly and surrounded by pericentriolar material, organize the cytoplasmic microtubule network during interphase, whereas during mitosis they form the bipolar spindle. In post-mitotic cells, the centrosome migrates to the cell surface, where the mother centriole differentiates into the basal body. This structure nucleates microtubules to form a primary cilium. The presence of a primary cilium on the cell surface is transient, limited to the quiescent G1 (G0) phase, as well as to the beginning of the S phase of the cell cycle. Disassembly of the primary cilium must precede mitosis. In asynchronous populations, typically 10% to 25% of cells have observable cilia. As cultured cells become quiescent, an increasing proportion of the population is ciliated, attaining >90% in some cell types [8]. In the G2 phase the microtubules of the primary cilium are resorbed and the centrosome migrates to the centre of the cell where it organizes the mitotic spindle. The term “centriole/basal body” is sometimes compared to the term “evening star/morning star”: the same organelle, when organizing the mitotic spindle in the centre of the cell, is called a centriole, whereas in the quiescent phase of the cell cycle, when anchored to the plasma membrane, forming the primary cilium, it is called a basal body [6]. Thus, it can never be in both places at the same time.
For a long time the primary cilium was considered to be a nonfunctional vestige. The function of the centriole has remained quite controversial for many decades. This controversy arose from the emphasis of the mitotic role of centrioles and marginalization of their role in the formation of the sensory primary cilium. There is ample experimental evidence and many observations to show that mitosis can proceed without centrioles in many cases [9, 10]; however, the primary cilium cannot exist without centrioles. With the new appreciation of the ubiquitous importance of the primary cilium in physiology, the hypothesis that centrioles primarily exist for the purpose of driving ciliogenesis seems to be quite acceptable [9]. Centrioles may be more important for the formation of the primary cilium than for mitotic spindle development. In an adult organism, the majority of cells exist in a quiescent state. Therefore, for a non-dividing cell, it is more important to respond to transient environmental signals sensed through the primary cilium than to prepare for mitosis. Thus, centrioles are only shortly “borrowed” to act as a mitotic organizing centre during mitosis in order to optimize cell division [11] [Scheme 2].

Scheme 2
Example of a cell cycle with a duration of 24 hours
In non-cancer cells, the centrosome is located asymmetricaly during interphase (22 hours), close to the plasma membrane, forming the sensory primary cilium, whereas during mitosis (2 hours) it forms the mitotic spindle.
In cancer cells, the centrosome is located close to nucleus during interphase (it can probably overcome the restrictions of the cell cycle connected to the primary cilium cycle), and during mitosis it forms the mitotic spindle.
Note: actual times for each phase depend on the tissue, the microenvironment and the physiological state.
Asynchronous growth and asymmetric signalling of primary cilia on the surface of sister cells according to the age of their centrioles/basal bodies

Centriole duplication in the G1(G0)/S phase results in two centrosomes, one with an older mother centriole and one with a new mother centriole; they are segregated during mitosis. It was observed that sister cells resulting from a mitotic division grow primary cilia asynchronously and that the sister cell receiving the older mother centriole usually builds its primary cilium first. The primary cilium on the sister cell with the older mother centriole is transiently longer and contains more receptors. These observations suggest that the segregation of differently aged mother centrioles, an asymmetry inherent in every animal cell division, can influence the ability of sister cells to respond to environmental signals, potentially altering the behaviour or fate of one or both sister cells. Asynchronous primary cilium growth can lead to differential responses of sister cells to an identical environmental signal. In the case of a signal that is transient (short period) or weak, the cell that bears the primary cilium first can respond to that signal, whereas its sister cell cannot [12].

Ciliary rootlet

The ciliary rootlet originates from the proximal end of the basal body, anchoring the cilium, and extends proximally towards the cell nucleus. Prominent rootlets are associated with sensory cilia of photoreceptor cells (sensors of electromagnetic field). In a photoreceptor, the rootlet appears as a very thick, striated filament that traverses the entire cell body all the way to the synaptic terminal [13]. The diameter of the rootlets of photoreceptor cells is approximately 80-100 nm, thus is the largest cytoskeletal structure in any mammalian cell. The rootlet is composed of homopolymeric rootletin protofilaments bundled into filaments. Rootletin (220 kD protein) has a globular head domain and a tail domain consisting of extended coiled-coil structures.
Ciliopathies
Primary cilia are key coordinators of signalling pathways during cell development and in tissue homeostasis. When defective, primary cilia are a major cause of human diseases and developmental disorders, which are now commonly referred to as ciliopathies.

Most cancer cells do not possess primary cilia, although there are some exceptions, such as tumours depending on the Hedgehog pathway, for example, basal cell carcinoma and medulloblastoma. The loss of primary cilia is a regular feature of neoplastic transformation in the majority of solid tumours [Scheme 2]. The primary cilium could serve as a tumour suppressor organelle [14].

Conclusion
The primary cilium is a microtubule-based structure protruding from the cell surface, functioning as a sensor for extracellular environmental signals that regulate cellular differentiation and division [11]. The presence of a primary cilium on the surface of the cell is transient, limited to the quiescent phase of the cell cycle. Defects in cilia cause a broad spectrum of human diseases known as ciliopathies [15]. The loss of primary cilia is a regular feature of neoplastic transformation in the majority of solid tumours. Most cancer cells do not possess primary cilia.

Acknowledgement: Supported by research projects MZO 00179906 and SVV 53251.

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