Seminars in Cell & Developmental Biology xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Seminars in Cell & Developmental Biology

journal homepage: www.elsevier.com/locate/semcdb

Review

Canonical and non-canonical Hedgehog signalling and the control of metabolism

Raffaele Teperino[a], Fritz Aberger[b], Harald Esterbauer[c], Natalia Riobo[d], John Andrew Pospisilik[a,*]

[a] Department of Epigenetics, Max-Planck Institute of Immunobiology and Epigenetics, Freiburg, Germany
[b] Department of Molecular Biology, University of Salzburg, Salzburg, Austria
[c] Department of Laboratory Medicine, Medical University of Vienna, Vienna, Austria
[d] Department of Biochemistry and Molecular Biology and Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA 19107, USA

ARTICLE INFO

Article history:
Available online xxx

Keywords:
Non-canonical Hedgehog signalling
Metabolism
Development
Cancer

ABSTRACT

Obesity and diabetes represent key healthcare challenges of our day, affecting upwards of one billion people worldwide. These individuals are at higher risk for cancer, stroke, blindness, heart and cardiovascular disease, and to date, have no effective long-term treatment options available. Recent and accumulating evidence has implicated the developmental morphogen Hedgehog and its downstream signalling in metabolic control. Generally thought to be quiescent in adults, Hedgehog is associated with several human cancers, and as such, has already emerged as a therapeutic target in oncology. Here, we attempt to give a comprehensive overview of the key signalling events associated with both canonical and non-canonical Hedgehog signalling, and highlight the increasingly complex regulatory modalities that appear to link Hedgehog and control metabolism. We highlight these key findings and discuss their impact for therapeutic development, cancer and metabolic disease.

Contents

Abbreviations: GLI1/2/3, glioma-associated oncogene homologue 1/2/3; PTCH, patched; SMO, smoothened; SUFU, suppressor of fused; CDO, CAM-related/downregulated by oncogenes; BOC, brother of CDO; GAS1, growth arrest-specific 1; PKA, protein kinase A; GSK3β, glycogen synthase kinase 3β; CK1, casein kinase 1; SAG, smoothened agonist; SHH, sonic Hedgehog; DHH, desert Hedgehog; IHH, Indian Hedgehog; GRK2, G-protein coupled receptor kinase 2; PTX, pertussis toxin; RAC1, Ras-related C3 botulinum toxin substrate 1; RHOA, Ras-homolog family member A; NF-kB, nuclear factor kappa-light-chain-enhancer of activated B cells; CARMA1, CARD-containing MAGUK protein 1; BCL10, B-cell CLL/lymphoma 10; MALT1, mucosa associated lymphoid tissue lymphoma translocation gene 1; LRP2, LDL-receptor-related-protein 2; VLDL, very low-density lipoprotein; HIF1α, hypoxia-inducible factor 1α; IGF1, insulin-like growth factor 1; IPF1/PDX1, insulin promoter factor 1/pancreatic and duodenal homeobox 1; PPARγ, peroxisome proliferator-activated receptor gamma; CAMKK2, calcium-calmodulin-dependent kinase 2; AMPK, AMP-dependent kinase; PKM2, pyruvate kinase M2 isoform; PDHa1, pyruvate dehydrogenase a1; CLD-Smo, ciliary localization deficient Smo; LKB1, liver kinase B1.

* Corresponding author. Tel.: +49 7615108793.
E-mail addresses: pospisilik@ie-freiburg.mpg.de, pospisilik@immunbio.mpg.de (J.A. Pospisilik).

http://dx.doi.org/10.1016/j.semcdb.2014.05.007
1084-9521/

1. The Hedgehog signalling pathway

Q3 Proper control of development, tissue homeostasis and metabolism of higher multicellular organisms is a delicate and highly complex process that relies on the precise temporal, spatial and context-dependent regulation of molecular signalling pathways. The importance of controlled signal activation and termination is critical to the function of essentially all organisms. In higher organisms, the failure to induce, attenuate or stop signalling precisely can result in severe developmental anomalies, metabolic disorders or life threatening malignant diseases [1–6].

Despite decades of molecular genetic advances, our understanding of the cues governing embryonic development and health of adult higher organisms comprises only a handful of signalling pathways. These include, but are not limited to Hedgehog, Wnt, Notch, Hippo, Jak/Stat, receptor-tyrosine kinases, and Tgfβ signalling cascades [7]. While few, these signalling appear able to control a plethora of context dependent biological processes.

The Hedgehog signal transduction pathway can be regarded as a paradigm of how a single, and at first glance, simple molecular cue (i.e. secreted Hedgehog protein bound to its receptor) selectively translates into an array of distinct cellular reactions depending on context [8,9]. To date, a number of fundamental principles have been uncovered that link pathway activation and functionally distinct cellular response. For instance, Hedgehog can behave as a morphogen, that is, increasing concentrations of Hedgehog ligand can elicit distinct cellular responses [10,11]. Also, numerous studies have highlighted the importance of molecular cross-talk between the Hedgehog and other signalling cascades, interactions that can modulate signal strength and determine specificity of molecular and cellular phenotypes [12–23].

Somewhat unique to Hedgehog signalling are the number and variety of modes by which the Hedgehog signal can be stimulated and transduced to impact the behaviour and fate of the target cells [24]. For simplicity, the different modes of Hedgehog signalling are mostly commonly classified as either canonical or non-canonical. Canonical Hedgehog signalling in vertebrates is most similar to the Hedgehog signal transduction mechanisms originally identified in the fruit fly. They involve Hedgehog-dependent activation of the Gli zinc finger transcription factors [25,26]. Non-canonical Hedgehog signalling is less well defined; a multiplicity of different modes have been documented without any simple, over-arching theme. Simply put, non-canonical Hedgehog signalling currently refers to Hedgehog co-receptor dependent signals that do not clearly act via the canonical Hedgehog-to-Gli route (Fig. 1 and [24]). Non-canonical Hedgehog signalling pathways have been classified in two groups: *Type I* signals that stem from the peptide ligand receptor Ptch, and *Type II* signals that stem from the seven trans-membrane domain containing G-protein coupled receptor (GPCR) Smo. In addition, Smo-independent activation of Gli has also been referred to as non-canonical Hedgehog signalling.

Here, after a brief overview of canonical signalling, we will focus on Smo-dependent, Gli-independent non-canonical Hedgehog signalling. We will summarize recent findings on the role of Smo as a GPCR regulating cytoskeletal architecture, cell motility, and axon guidance, as well as highlighting a novel regulatory link to the maintenance of cellular and organismal energy homeostasis.

1.1. Canonical Hedgehog signalling

Canonical Hedgehog signalling was first discovered in *Drosophila*, where seminal work on embryonic patterning mutants led to the identification of the *hedgehog* gene. Loss of Hedgehog function in the fly results in a disorganized lawn of spiky processes and denticles on the surface of the fly larva, a Hedgehog-like phenotype that coined the name of the pathway [27]. While

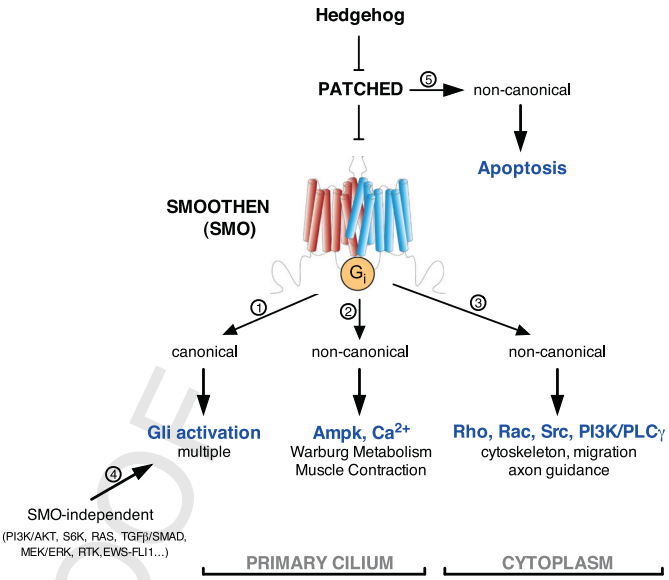

Fig. 1. Q5

canonical Hedgehog signal transduction is highly conserved, several key differences have emerged since the divergence of flies and mammals. Included, are a critical negative regulatory function of vertebrate Sufu, and an expansion of the activator and repressor repertoire of the fly transcription factor *Cubitus interruptus* to three distinct zinc finger transcription factors, Gli1, Gli2 and Gli3, in vertebrates [8,28–30]. The primary cilium, commonly thought to be a prerogative of Hedgehog signalling in vertebrates, has also been shown to play a central role in flies [31,32].

Vertebrate canonical Hedgehog signalling is initiated by binding of proteolytically processed and lipid modified Hedgehog ligand to its receptor Patched (Ptch), a twelve-pass transmembrane protein that represses the pathway in the absence of ligand [33–37]. Three distinct co-receptors, Cdo, Boc, and Gas1, facilitate high-affinity binding of mature Hedgehog ligand to Ptch, thereby enhancing Hedgehog signal strength [38–42].

Ligand binding to Ptch abrogates its repressive effect on the seven-pass transmembrane protein Smo, a key effector essential for canonical Hedgehog signal transduction [43]. The repressive role of ligand-free Ptch depends on its localization in the primary cilium, a single antenna-like structure that protrudes from the cell surface of most adherent cell types and functions as an organizer-like signal transduction compartment. Ciliary Ptch prevents pathway activation by blocking the entry of Smo into the primary cilium. Binding of Hedgehog protein to Ptch removes Ptch from the primary cilium, thereby allowing Smo to enter and, upon an unknown activation step, propagate the Hedgehog signal further downstream [28,44,45]. Despite intense efforts to understand Ptch function, the detailed mechanisms of how Ptch represses Smo in the absence of ligand is still elusive. Ptch contains a sterol-sensing domain and belongs to the family of RND (Resistance-Nodulation-cell Division) transporters [46]. Several functional studies support a model where Ptch prevents Smo activation either by removing Smo agonists such as oxysterols from the primary cilium or by increasing the influx of Smo antagonists into the cilium [47–50]. In addition, Ptch may also modify the lipid composition of Smo-containing endosomes and therefore negatively control Smo trafficking towards the primary cilium [51,52].

The key role of Smo in canonical Hedgehog signalling is to control the activation of the Gli zinc finger transcription factors [53]. Of note, the Gli family member Gli3, and to some extent also Gli2, exerts a dual function as transcriptional repressor (GliR)

Please cite this article in press as: Teperino R, et al. Canonical and non-canonical Hedgehog signalling and the control of metabolism. Semin Cell Dev Biol (2014), http://dx.doi.org/10.1016/j.semcdb.2014.05.007