We are IntechOpen,
the world's leading publisher of
Open Access books
Built by scientists, for scientists

4,800
Open access books available

122,000
International authors and editors

135M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

BOOK CITATION INDEX
CLARIVATE ANALYTICS
INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Signalling Pathways in Development and Human Disease: A Drosophila Wing Perspective

Cristina Molnar, Martín Resnik-Docampo, María F. Organista,
Mercedes Martín, Covadonga F. Hevia and Jose F. de Celis
Centro de Biología Molecular "Severo Ochoa", CSIC and UAM
C/Nicolás Cabrera 1, Universidad Autónoma de Madrid, Madrid
Spain

1. Introduction

The proteins involved in signalling are organised in several signalling pathways, and both these proteins and their molecular interactions are conserved during evolution. In this chapter we describe the genetic structure of the main conserved signalling pathways identified in multicellular organisms, focusing in those signalling pathways in which the activation of cell receptors by proteins with ligand activity is linked to transcriptional responses. These pathways play key roles during normal development, and their de-regulation has been implicated in a variety of human diseases. We will emphasize the conservation of the proteins and mechanisms involved in each of these pathways, and describe the Drosophila wing imaginal disc as an experimental system to dissect cell signalling in vivo. Finally, we will discuss some of the strategies that are been used to identify additional components of signalling pathways in Drosophila. Our main aim is to underline the general structure of signalling pathways, the relevance of signalling for normal development and for the appearance of multitude of human diseases, and describe several strategies that Drosophila genetics offers in biomedical research.

2. General structure of signalling pathways in multi-cellular organisms: Ligands, receptors, transducers and transcriptional outputs of the Notch, EGFR, InR, Wnt, TGFβ, BMP, Hippo and JNK pathways

Signalling pathways are molecular modules used to convey information among cells. Each pathway is formed by several components connected by molecular recognition and organised in a hierarchical manner, starting with a ligand and ending with a transcription factor. The temporal and spatial expression of the ligands determines the domain of activation of each signalling pathway. The expression of ligands is subject to transcriptional regulation defined by the combination of transcription factors present in the ligand-producing cell (see for example Bachmann and Knust, 1998; Haenlin et al., 1990; Haenlin et al., 1994; Parks et al., 1995; Vargesson et al., 1998). The outcome of each pathway is the activation of a specific transcription factor, and consequently, in many respects a signalling pathway is a molecular device used to coordinate gene expression programs in cell populations. In these roles they are instrumental during multicellular development and

adult tissue homeostasis, regulating a variety of cell behaviours including cell division, apoptosis, migration and differentiation.

The components of each signalling pathway can be operationally grouped into ligands, receptors, transducers and transcription factors (Table 1).

Pathway/Organism	Ligands		Receptors		Transducers		Transcription Factors	
	Fly	Human	Fly	Human	Fly	Human	Fly	Human
EGFR	Argos Spitz Vein Gurken Keren	Argos EGF HB-EGF TGF-a NRG1-4 EPR	EGFR Sevenless Torso	EGFR ROS1 HER 2-4	Sos Grb Ras Raf dMEK rolled dPI3K dPTEN dPDK1 AKT	Sos1 Grb2 K-Ras /H-Ras/N-RAS SHC MEK 1/2 MEKK 1/3 ERK 1/2 PI3K PTEN PDK1 AKT	Yan Pointed 1-2	ETV ETS (ELK1) AP1 SRF
SWH	dachsous	DCHS 1 DCHS 2	Fat CRB	Fat 1-3 Fat 4	Hippo Salvador Kibra Expanded Merlin Mats Warts dRassf1 Dachs	MST1,2 hWW45/SAV1 Kibra Willin/FRMD6/Ex2 MER/NF2 MOBK1B LAT 1-2 RASSF1	Yorkie	YAP,TAZ
NOTCH	Delta Serrate	Delta-4/A-D Serrate Jagged1-2 Dll3-4	Notch	Notch1 Notch2-4			Su(H) Notch-i	CSL NICD
InR	Ilp1-7	Insulin IGF1-3	InR	IGF1R	dPI3K dPTEN dPDK1 AKT dRheb dTSC1/2	PI3K PTEN PDK1 AKT Rheb TSC1/2	dFOXO	FOXO
TOR	Leucine Glutamine	Leucine Glutamine	Slimfast pathetic	 SLC7AS/SLC3A2	dRagA/C dMAP4K3 dTOR draptor drictor dS6K d4EBP1	RRAG B/C hMAP4K3 TOR Raptor Rictor S6K 4EBP1	Tif-IA	UBF TIF-1A SL1 Pol I
JNK	Eiger PVF	TNF PDGF	Wengen PVR	TNFR1 TNFR2 PDGFR	dTRAF1-2 dRac1 Msn Dsh MAP4K3 dTAK1 dASK1 Slpr dMekk1 Hep BSK	TRAF1-2 Rac1 MAP4K3 TAK1 ASK1 MEKK1/4 MKK4/7 JNK1/2/3	Jra Kayak	Jun Fos
TOLL	Spaetzle		Toll	TLR1,2,4,5,6,11	Pelle Cactus kinase Tube Pellino Myd88 Gprk2	IRAK1,3 MYD88 TIRAP IRAK4 TRAF6 TAK1 TAB1 MKK3-4/6-7 TBK1 IRF3,7	Dif/Dorsal Deaf1	NFKB1 DEAF1
JAK/STAT	Upd 1-3	IFN I (a/b) IFN II (g)	Dome Mom	Gp130	Hop	JAK1/2/3 TYK2	 STAT92E	STAT1a/ b STAT2 STAT3a/b STAT4a/b STAT5A /B/6

Continuation	Ligands		Receptors		Transducers		Transcription Factors	
Pathway/Organism	Fly	Human	Fly	Human	Fly	Human	Fly	Human
WNT	Wingless	WNT 1 WNT 2-16	Frizzled Arrow	Frizzled LRP 5 LRP 6 ROR2	Dishevelled Axin Zeste-White 3 APC Armadillo	Dishevelled Axin GSK3 APC b-Catenin DVL	Pangolin	LEF/TCF
TGF-β	Dpp Gbb Activinb Scw Daw Mav Myo	BMP2,4 BMP5-8 Activin A,B TGFb1,2,3 Nodal GDF 5 MIS	Tkv Sax Wit Babo Put	BMPR IA,IB ALK-1,2,6 ActRIB/AcvR-i/ALK4/TbRI BMPR-II/ TGbR-II/ AMHR ActR-II, IIB	Mad dSmad2 Medea Dad	Smad1,5,8 Smad2,3 Smad4,4b Smad6,7	Mad dSmad2 Medea	Smad1,5,8 Smad2,3 Smad4,4b
Hh	hh	Shh Ihh Dhh	Ptc	Ptc1 Ptc2	Smo Costal2 Fused Su(Fu) PKA CKI GSK3 Kurtz Slimb Gprk2	SMO KIF7 KIF3A IFT88/IFT172 Fused SUFU MIM Iguana FKBP8 SIL Rab23 PKA CKI GSK3 b-arrestin-2 {beta}TrCP GRK2	Cubitus-i	Gli-1 Gli-2,3

Table 1. Main components of the principal signalling pathways in *Drosophila melanogaster* and *Homo sapiens*.
For references see: EGFR: Kataoka, 2009/Shilo, 2003; SWH:Gruscne et al., 2010/Kango-Singh and Singh, 2009/Matallanas et al., 2008; Notcn:Bray 2006/Scnwanbeck et al., 2010; InR: Ma and Blenis, 2009; TOR: Hietakangas and Cohen, 2009/Rosner et al., 2008/Zoncu et al 2011; JNK: Igaki 2009- Toll' So and Oucni 2010/ Valanne et al., 2011; JAK/STAT: Rane and Reddy, 2000/Hou et al., 2002/Wright et al., 2011; Wnt: Seto and Bellen, 2004/Chien et al., 2009; TGF-B: Raftery and Sutherland, 1999/Massague and Wotton, 2000/Waite and Eng, 2003 and Hh: Ruiz-Gomez et al., 2007/Jacob and Lum, 2007.

In the simplest example, that of steroid hormones, a single protein can recognise a ligand molecule and also acts as a transcription factor (Stanisic et al., 2010), but, in general, different proteins can be unequivocally assigned to each category in different pathways. Ligands are mostly proteins that can be secreted from the cell or directly presented in the cell membrane to neighbouring cells (Figure 1). In general, ligands are subject to considerable post-transcriptional modifications, including ubiquitination (Delta/Serrate in the Notch pathway; Le Bras et al., 2011), lipid modifications (Hedgehog family of proteins; Steinhauer and Treisman, 2009), proteolytic processing from a larger precursor to form the active peptide (TGFß superfamily members and EGF/FGF ligands; Zhu and Burgess, 2001; Urban et al., 2002), palmitoylation and glycosylation (Wnt and EGFR ligands; Miura et al., 2006; Steinhauer and Treisman, 2009) and glycosylation (JAK/STAT ligands) (Figure 1). These modifications are required for the secretion of the ligand and its spreading through the tissue, and they also determine their ability to bind and activate their receptors. In addition,
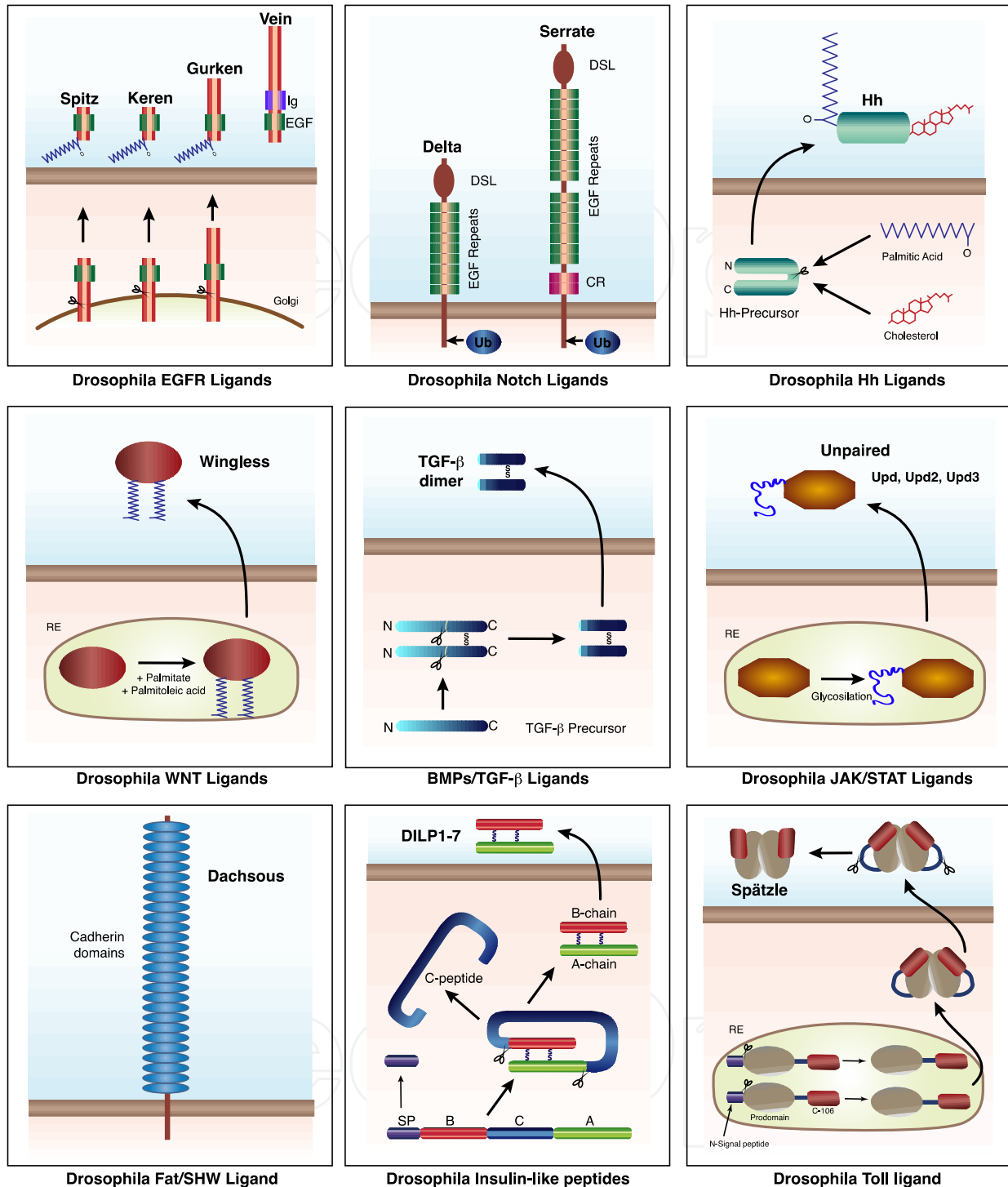
Fig. 1. Schematic representation of the ligands and their post-transcriptional modifications. Upper panels: EGFR, Notch and Hh ligands, middle panels: Wnt, BMP/TGFβ and JAK/STAT ligands and bottom panels (SWH, Insulin and Toll ligands.

most secreted ligands display strong interactions with several components of the extracellular matrix, which help to establish their diffusion range and to shape the concentration of active ligand at a distance from the ligand-producing cells (Jackson et al., 1997; Baeg et al., 2001; Araujo et al., 2003; Bartscherer and Boutros, 2008). The distribution of

the ligands is also affected by interactions with their receptors, as ligand-receptor interactions remove the ligand from the extra-cellular milieu and regulate the concentration of the ligand through endocytosis and subsequent lysosomal degradation or recycling of ligand-receptor complexes (Lecuit and Cohen, 1998; Chen and Struhl, 1996; Funakoshi et al., 2001; Pfeiffer and Vincent, 1999).

Receptors are in general transmembrane proteins with two well-differentiated activities. Thus, they interact with the ligand through their extra-cellular domain, and recruit different components of the transduction machinery in their intra-cellular domain (Figure 2). The cell biology of receptors is complex and diverse, but in general includes mechanisms to ensure the correct trafficking of the receptor through the Endoplasmic reticulum-Golgi network, post-transcriptional modifications during trafficking to synthesize the active form of the protein, localization of the receptor to apical domains in the cell membrane, interaction of the receptor with different co-receptor molecules, and turn-over mechanisms that regulate the number of activated-receptors in the cell membrane and other intracellular compartments (Piddini and Vincent, 2003; Hoeller et al., 2005; Mills, 2007; Sorkin and von Zastrow, 2009; Bethani et al., 2010). Similarly, the activation of the receptor by binding to appropriate ligands uses different mechanisms that rely in the clustering of receptor complexes, phosphorylation of receptor molecules after complex formation (EGFR and TGFß), or conformational changes that allow the proteolytic processing of the receptor (Notch) or its interaction with specific transduction components (Wnt; Figure 2).

The receptors act on their downstream transducers through a variety of mechanisms that include phosphorylation (EGFR/InR and JAK; Arbouzova and Zeidler, 2006; Pfeifer et al., 2008; Hombria and Sotillos, 2008 Avraham and Yarden, 2011) and TGFß receptor complexes; Miyazono et al., 2010), the recruitment of intracellular transducers after conformation changes (Wnt receptors; Angers and Moon, 2009), or the indirect modification of the phosphorylation state and subcellular localization of its transducer (Hedgehog receptors; Ruiz-Gomez et al., 2007). In a particular case (Notch; Bray, 2006), the receptor itself directly contributes to modify the composition and activity of transcription complexes (Figure 2).

The components of the transduction machinery downstream of the receptor are also heterogeneous, ranging from the simplest cases in which the receptor itself becomes part of a transcription complex (Notch) or directly modifies by phosphorylation a transcription factor, triggering a change in its subcellular localization from the cytoplasm to the nucleus (Smad and Stat proteins in TGFβ and JAK pathways, respectively; Miyazono et al., 2010; Hou et al., 2002). In other cases the receptor (Wnt receptors; Angers and Moon, 2009) or a transducer regulated by the receptor (Smoothened in the Hh pathway; Ruiz-Gomez et al., 2007) acts as a scaffold to recruit and sequester different components that prevent the accumulation of a transcription factor in the nucleus (ß-catenin and Gli, respectively). Finally, in the cases of Sav/Warts/Hippo (SWH; Harvey and Tapon, 2007; Halder and Johnson, 2011), Toll (Valanne et al., 2011), and receptors with tyrosin-kinase activity such as EGFR (Shilo, 2003) and InR (Brogiolo et al., 2001), the activation of the receptor is communicated to the responding transcription factor through a linear cascade of phosphorylation (EGFR, InR and SWH) or proteolytic events (Toll) that end in the generation of active forms of the transcription factor localised in the nucleus (ETS proteins for EGFR and Rel/Dorsal for Toll), or in the exclusion from the nucleus of the transcriptional co-activator Yorki/YAP (SWH) (Table 2).

By using these mechanisms, the state of the pathway changes the nuclear localization of a transcription factor that binds to the DNA with sequence–specificity. In the simplest cases
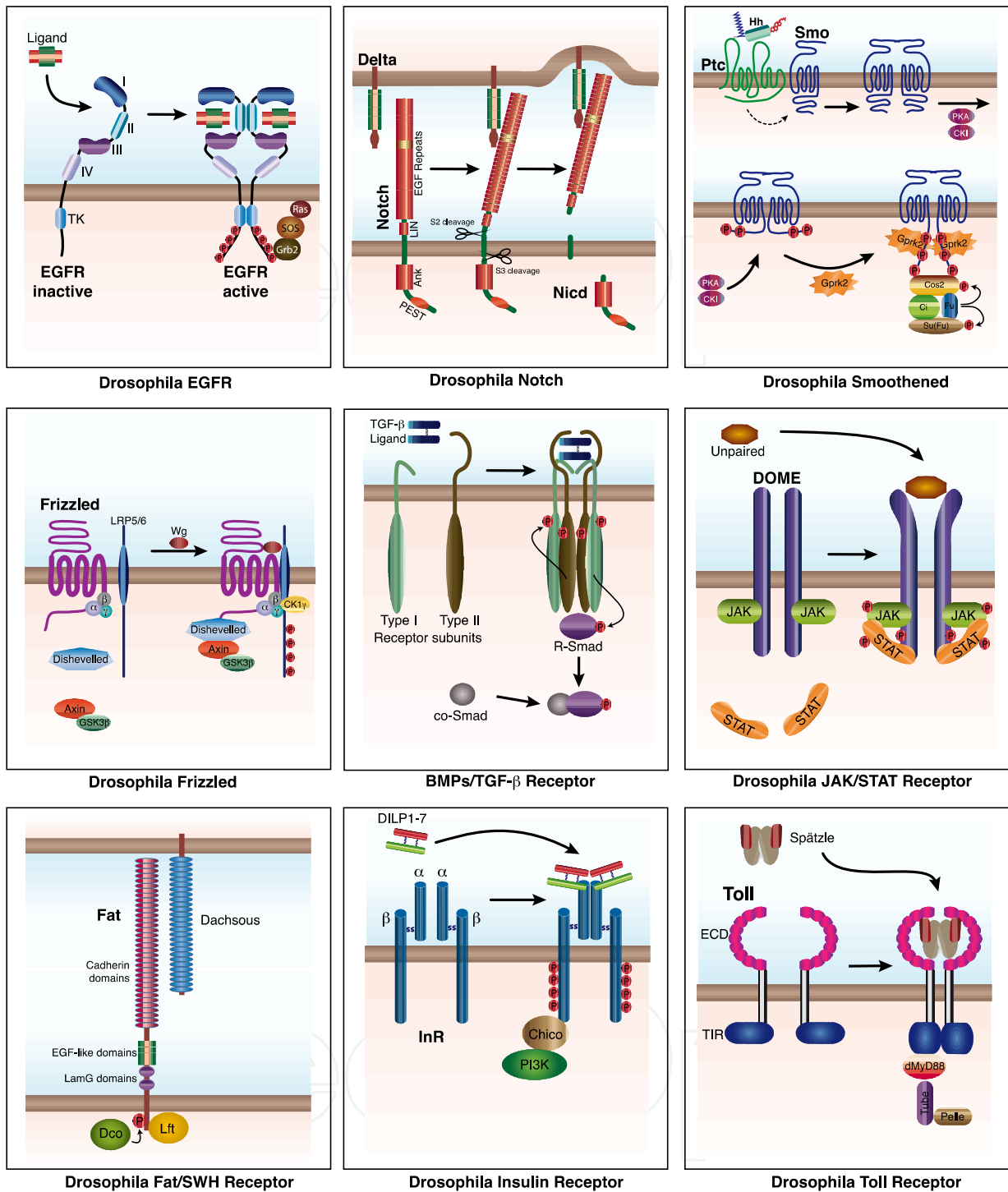
Fig. 2. Schematic representation of the receptors and their mechanisms of activation

this is accomplished directly by the receptor itself, which re-localise to the nucleus upon ligand binding (Notch). In the case of Yorki/YAP (SWH; Harvey and Tapon, 2007) and Foxo (InR; Van Der Heide et al., 2004; Greer and Brunet, 2008), pathway activity prevents or promote, respectively, their entrance into the nucleus, and in the case of Dorsal/Rel (Gerondakis et al., 2006) the pathway triggers the proteolytic processing of a protein that sequesters this transcription factor in the cytoplasm (Table 2). In other pathways the

transcription factor resides in the nucleus, where it acts as a member of a transcriptional repressor complex. In these cases, the transcriptional output of signalling is determined by the induction of a transition, regulated by the pathway, from a transcriptional repressor to a transcriptional activator (Table 2). This transition is accomplished using different mechanisms such as the generation of an intracellular fragment of the receptor (Notch; Bray, 2006), the phosphorylation of the transcription factors (ETS in EGFR; Baonza et al., 2002 and Smads in TGFß; Miyazono et al., 2005) or the inhibition of the proteolytic processing of the transcription factor (Gli in Hh and ß-Catenin in Wnt: Nusse, 1999).

Pathway / Organism	TF		Activation of TF		Localization/State of TF		Co-TF	
	Fly	Human	Fly	Human	Fly	Human	Fly	Human
EGFR	Pnt/Yan	ETS/ETV	Phosphorylation		C/N; R/A		Gro MAE	TLE -
Hh	Ci	Gli-1, Gli-2, Gli-3	Proteolisis		C/N; R/A		dCBP	CBP
InR/TOR	dFOXO	FOXO	Phosphorylation		N/C; R/A			-
JAK/STAT	Stat92E	STAT1-2-3-4-5-6	Phosphorylation		C/N; A		Ept	TSG101
JNK	Jra/Kay	Jun/Fos	Phosphorylation		C/N; A			-
NOTCH	Su(H)-NICD	CSL-NICD	Proteolisis		C/N; R/A		Mam -	MANL1-3 SKIP
SWH	Yki	Yap, Taz	Phosphorylation		N/C; A		Sd Hth	TEAD1-4 Meis1-3
TGFβ	DSmad2-Med/Mad-Med	Smad2-Smad4/Smad3,Smad5-Smad4	Phosphorylation		C/N; R/A		Shn dCBP dSki/dSno	HIVEP3 CBP SKIL
TOLL	Dif/Dorsal	NFκβ	Proteolisis		C/N; A		dCBP Gro TAF$_{II}$60/TAF$_{II}$110 Twi	CBP TLE TAF6 TWIST1
WNT	Arm-Pan	β-catenin-TCF	Proteolisis		C/N; R/A		Gro dCBP Lgs Brm	TLE CBP BCL9L BRG1

Table 2. Transcription factors and their mechanism of activation. Abbreviations: Transcription Factor (TF), Pointed (Pnt), Cubitus interruptus (Ci), Signal-transducer and activator of transcription protein at 92E (Stat92E), Jun-related antigen (Jra), Kayak (Kay), Suppressor Hairless (Su(H)), Notch intracellular domain (NICD), Yorki (Ykl), Mothers against dpp (Mad), Medea (Med), Dorsal-related inmmunity factor (Dif), Armadillo (Arm), Pangolin (Pan), Groucho (Gro), CREB-bincing protein (CBP), Erupted (Ept), Tumor Susceptibility Gene-101 (TSG101), Mastermind (Mam), Skl-interacting Protein (SKIP), Scalloped (Sd), Homothorax (Hth), Schnurri (Shn), Human immunodeficiency virus type I enhancer binding protein 3 (HIVEP3), Sno oncogene (Sno), SKI-like oncogene (SKIL), TBP-associated factor "60/110 (TAF"60/110), Twist (Twi), Legless (Lgs), Brahma (Brm). Localization/State of TF: Citosolic (C) and nuclear (N) subcellular localization. Function as a transcriptional activator (A) or repression (R). TF that traslocate to the nucleus upon activation (C/N) or from the nucleus to the cytoplasm (N/C). For references see: EGFR: Vivekanand et al., 2004/Hassen and Paroush, 2007; Hn: Akimarti et al., 1997a/Chen et al., 2000; InR/Tor: Ma and Blenis, 2009/Hietakangas and Cohen, 2009/Resnik-Docampo and de Celis, 2011; JAK/STAT: Gilbert et al., 2009 ; JNK: Igaki, 2009; NOTCH: Zhou et al., 2000/Petcherski and Kimble, 2000/Bray, 2006; SWH: Halder and Johnson, 2011; TGFb: Feng et al., 1998/Janknecht et al., 1998/Pouponnot et al., 1998/Waltzer and Bienz, 1999/Luo et al., 1999/Strochein et al., 1999/Sun et al., 1999a/Sun et al., 1999b/Dai et al., 2000/Barrio et al., 2007; Toll: Dubnicoff et al., 1997/Aklkmaru et al., 1997b/Pham et al., 1999 and Wnt: Waltzer and Bienz, 1998/Roose et al., 1998/Nusse, 1999/Barker et al., 2001/Hoffmans and Basler, 2004.

In all cases, the presence in the nucleus of a transcriptional activator in response to signalling modifies the expression of a battery of target genes, leading to changes in cell behaviour that are conditioned by the state of the responding cell. In this manner, some aspects of the transcriptional landscape of the ligand expressing cells are communicated to the receiving cells, where a novel pattern of transcription can be established. Thus, the transcription factors regulated by each signalling pathway contribute to the combinatory of regulators present in a given cell, and this, combined with the structure of gene regulatory sequences, makes the transcriptional responses to a pathway cell type specific (Bonn and Furlong, 2008; Chopra and Levine, 2009). At this time, little is known about the number and identity of target genes whose expression are directly regulated by signalling and whose function contributes significantly to the cellular response to signalling. This is an area of intensive research, and the use of chromatin immunoprecipitation techniques coupled with microarrays or deep-sequencing, the development of reporter systems for cell culture assays and the functional analysis of the identified target genes promise a much better understanding of the transcriptional responses to signalling in the near future (Yang et al., 2004; Miyazono et al., 2005; Friedman and Perrimon, 2006; Mummery-Widmer et al., 2009; Bernard et al., 2010; Kim and Marques, 2010).

3. General aspects of the biological roles play by signalling pathways during development

The development of multicellular organisms relies to a large extent in the spatial and temporal generation of gene expression domains (Arnone and Davidson, 1997). In this manner, and under the perspective that signalling pathways are mostly elaborate devices to regulate transcription, it is no wonder that these pathways play prominent roles during the development of all organisms. Their key contribution is mostly based in their ability to communicate transcriptional stages between cell populations and generate spatial domains of gene expression. Other characteristics that make signalling a powerful system to regulate cell behaviour are the quantitative response to signalling, the operation of elaborate feed-back mechanisms, positive and negative, that modulate the intensity and duration of signalling (Perrimon and McMahon, 1999), and the existence of cross-interactions between pathways (McNeill and Woodgett, 2010). These cross-interactions occur both at the level of transcription, in which one pathway regulates the expression of others pathway ligands, or by interactions in which one pathway affects the activity of components belonging to a different pathway (Hasson and Paroush, 2007; McNeill and Woodgett, 2010). All these characteristics confer a great versatility to the function of signalling during development, and also contribute to the disastrous consequences that signalling miss-regulation has in different genetic disorders (Harper et al., 2003; Logan and Nusse, 2004; Inoki et al., 2005; Bentires-Alj et al., 2006; Jacob and Lum, 2007; Gordon and Blobe, 2008; Rosner et al., 2008; Gordon and Blobe, 2008; Table 3). To summarize, we have divided the biological roles played by signalling into the following categories:

1.   Cellular responses that directly modify the metabolic state of the cell. This is best exemplified by the action of the InR/TOR pathway, which activity is used as a way to adjust the growth of the cell to the availability of nutrients (Brogiolo et al., 2001). In addition, this pathway is also used to coordinate the growth of different organs during development and adult tissue homeostasis (Zoncu et al., 2011).

2. Cellular responses that make cells to progress through the cell cycle, acquire migratory behaviour, enter into the apoptotic pathway or in general to make a transition between cell states. All pathways contribute in different cellular settings to modify a pre-existing cellular state (Thompson, 2010). For example, inputs from the BMP and FGF pathways regulate the entrance in apoptosis of inter-digital epidermal cells during vertebrate limb development (Pajni-Underwood et al., 2007); and TGFß/BMPs also participate in regulating epithelial-mesenchymal transitions (Zavadil and Böttinger, 2005). BMP together with JNK also promote changes in the cytoskeleton that influence the movement of layers of cells during morphogenesis (Fernandez et al., 2007). On the other hand, several pathways have direct links with the cell cycle, either promoting the transitions between different phases of the cycle or triggering the entrance of cells in senescence (Campisi and d'Adda, 2007; Jones and Kazlauskas, 2001).

3. Regulation of alternative cell fates within populations of competent cells. Many pathways are engaged in the allocation of cell fates during development. The Notch and EGFR pathways fall in this class, regulating neural fates within proneural clusters in a process that employs Notch signalling to prevent neural fate and EGFR to promote this fate (Lage et al., 1997; Bray, 2006; Axelrod, 2010).

4. Regulation of spatial domains of gene expression within growing epithelia. The patterning of epithelial tissues is generally organised with respect to signalling centres. These centres operate as the source of ligands belonging to the EGFR, TGFß/BMP, Wnt and Hh signalling pathways. Because these ligands act in a concentration-dependent manner at a distance from the cells expressing them, they can set adjacent domains of gene expression that partition the epithelium into different territories with specific gene expression patterns. This process is used reiteratively during the development of all multicellular organisms, and some examples are the patterning of segments in the embryonic epidermis and the subdivision of the imaginal discs into different territories in flies (Moussian and Roth, 2005), the generation of cell diversity in the vertebrate neural tube (Lupo et al., 2006), the establishment of the antero-posterior patterning in the vertebrate limbs and many others (Kumar, 2001; Duboc and Logan, 2009; Towers and Tickle, 2009; Arnold and Robertson, 2009).

5. Interactions between independent layers of cells. The development of tridimensional structures implies the coordination of cellular fates between cell layers of independent origin. This type of information transfer is at the base of the chains of inductive processes that pervade vertebrate development, and also contribute to set temporal and spatial patterns of cell migration during neurogenesis and myogenesis (Carmena et al., 1998; Kimelman, 2006; Lupo et al., 2006; Wackerhage and Ratkevicius, 2008; Steventon et al., 2009; Mok and Sweetman, 2011).

The correct regulation of cell proliferation, differentiation and survival is essential for the proper development and homeostasis of all organisms. The key roles that signalling plays in these processes are likely behind the multitude of human diseases caused by genetic alterations in the components of most signalling pathways. We outlined in Table 3 some examples illustrating human pathologies associated to defects in signalling, showing that changes in the activity of almost any component of different pathways, from the ligands to the transcription factors, lead to specific pathologies. In this manner, both loss and gain of function mutations in different pathways have been described as potential causes of developmental disorders and disease. For example, the loss of TGFß and SWH function, as

well as increase in JAK/STAT and EGFR, Wnt and Hh signalling are linked to tumour formation and progression in a variety of cell types (Massague et al., 2000; Waite and Eng, 2003; Harvey and Tapon, 2007), the miss-regulation of Toll signalling is related with defects in the immune response (O'Neill, 2003), and is associated to the increase in the susceptibility of immune diseases such as Lupus and arthritis (Constantinescu et al., 2008; Schindler, 2002). Mutations in Hh, TGFß and Notch pathways have also been related with blood and circulatory system diseases such as hypertension or CADASIL, and defects in JNK pathway to neurodegenerative diseases including Parkinson and Alzheimer. Similarly, the mTOR pathway is implicated in metabolic diseases including diabetes and obesity as well as in ageing (Inoki et al., 2005). Finally, many developmental disorders, including Noonan syndrome, Cleft palate, Pallister Hall syndrome, Polydactyli or Tetra-Amelia, have been found associated to EGFR, TGFß, Hh, and Wnt de-regulation (Tartaglia and Gelb, 2005).

Pathway	Component		Disease	References
EGFR	Receptors	EGFR	Most carcinomas (including Breast, Ovarian and Stomatch)	Downward, 2003; Mendelsohn and Baselga, 2000; Kuan et al., 2001
		HER2	Breast cancer	Downward, 2003
	Transducer	B-Raf	Cardio-fascio-cutaneus syndrome, Colorectal cancer, Melanoma	Downward, 2003; Schubbert et al., 2007; Bentires-Alj et al., 2006
		Sos1	Noonan syndrome, JMML	Schubbert et al., 2007
		K-Ras	AML, JMML, Noonan, Myelodysplastic, Cardio-fascio-cutaneus and Leopard syndromes, Lung adenocarcinoma, Bladder, Colorectal, Kydney, Liver, Pancreas, and Thyroid tumors, Seminoma, Melanoma	Schubbert et al., 2007; Tartaglia and Gelb, 2005; Bentires-Alj et al., 2006; Downward, 2003; Bos, 1989
		H-Ras	AML, Costello and Myelodysplastic syndromes, Rhabdomyosarcoma, Neuro and Ganglioneuroblastoma, Adenocarcinoma, Bladder, Colorectal, Kydney, Liver, Lung, Pancreas and Thyroid cancers, Seminoma, Melanoma	Schubbert et al., 2007; Aoki et al., 2005; Bentires-Alj et al., 2006; Downward, 2003
		MEK 1/2	Cardio-fascio-cutaneus syndrome	Schubbert et al., 2007; Bentires-Alj et al., 2006
		C-Raf	AML	Zebisch et al., 2006; Kim and Choi, 2010

Pathway	Component		Disease	References
Hh	Ligand	Shh	Basal cell carcinoma	Beachy et al., 2004
	Receptor	Ptc1	Basal cell carcinoma, Medulloblastoma, Rhabdo and Fibrosarcoma	Taipale and Beachy, 2001; Peacock et al., 2007; Wechsler-Reya and Scott, 2001; Jacob and Lum, 2007
	Transducer	SUFU	Basal cell carcinoma, Medullobastoma	Beachy et al., 2004
		Smo	Basal cell carcinoma, Sporadic tumours, Medulloblastoma	Taipale and Beachy, 2001; Beachy et al., 2004; Peacock et al., 2007
	TF	Gli	Glioma, GCPS, PHS, PAP-A	Ruiz i Altaba et al., 2002; Beachy et al., 2004; Ruiz-Gomez et al., 2007; Zhu and Lo, 2010
InR	Ligand	IGF1	Colorectal neoplasia	Jacobs, 2008
		IGF2	Colonic adenocarcinoma	Jacobs, 2008
	Receptor	IGF2R	Breast and Hepatocellular carcinomas	Jacobs, 2008
	Transducer	PKD1	Polycystic kidney disease	Rosner et al., 2008
		PTEN	Bannayan-Riley-Ruvalcaba and Proteus syndromes, Cowden and Lhermitte-Duclos diseases	Inoki et al., 2005
		TSC 1/2	Tuberous sclerosis and Lymphangiomatosis	van Slegtenhorst et al., 1997; Rosner et al., 2008
		STK11	Peutz-Jeghers syndrome	Hernan et al., 2004
		AMPK	Cardiac hypertrophy	Blair et al., 2001
		VHL	Angiomas, Hemangioblastomas, Renal carcinoma	Rosner et al., 2008
TOR	Transducer	MAP4K3	Pancreas cancer	Zoncu et al., 2011
		mTORC1	Obesity	Zoncu et al., 2011
		S6K1-IRS1	Diabetes type 2	Zoncu et al., 2011
		NF1	Neurofibromatosis	Zoncu et al., 2011
		p14	Growth defects, Inmunodeficiency	Zoncu et al., 2011

Pathway	Component			Disease	References
JAK/ STAT	Receptor		IL-2Rgc	X-linked SCID	O'Sullivan et al., 2007
			IL-7Ra	SCID	O'Sullivan et al., 2007
			IFNgRI	Susceptibility to Mycobacterial infection	O'Sullivan et al., 2007
	Transducer		JAK2	ALL, AML, MPDs, PV, SCID	Constantinescu et al., 2008
			JAK3		Schindler, 2002; O'Sullivan et al., 2007
	TF		STAT1	ALL, AML, CLL, Brain, Breast, Lung, Head and Neck tumours, Erytroleukemia, Susceptibility to Mycobacterial infection	Bromberg, 2002; O'Sullivan et al., 2007
			STAT3	AML, CLL, LGL, Crohn's disease, Brain, Breast, Head, Lung, Neck, Ovarian, Pancreas, Prostate and Renal tumours, Mycosis fungoides, Burkitt's, Hodgkins and Anaplastic large cell lymphomas, Myeloma, Melanoma	Bromberg, 2002; O'Sullivan et al., 2007
			STAT4	Chronic obstructive pulmonary disease	O'Sullivan et al., 2007
			STAT5	ALL, AML, CML, Crohn's disease, Erytroleukemia	Bromberg, 2002; O'Sullivan et al., 2007
JNK	Transducer		JNK1	Diabetes type 2	Waeber et al., 2000
			JNK2	Atherosclerosis	Ricci et al., 2004; Sumara et al., 2005
			JNK3	Parkinson Disease	Resnick and Fennell, 2004
			p38	Alzheimer Disease	Smith et al., 2006
			MKK4	Breast, Biliary and Pancreatic carcinomas	Su et al., 1998
Notch	Ligand		Dll-3	Spondylocosta dysotosis	Harper et al., 2003
			Jagged-1	Alagille Syndrome	Harper et al., 2003
	Receptor		Notch-1	ALL	Ellisen et al., 1991; Harper et al., 2003
			Notch-3	CADASIL	Harper et al., 2003
			Notch-4	Lung Cancer, Esquizophrenia and Aloppecia aerata	Dang et al., 2000; Wei and Hemmings, 2000; Ujike et al., 2001; Tazi-Ahnini et al., 2003

Pathway	Component		Disease	References
TGFβ	Ligand	TGFβ	Mammary, Prostate and Renal cancers	Rooke and Crosier, 2001
		TGF1	Camurati-Englemann disease	Gordon and Blobe, 2008
		GDF-5	Hunter-Thompson and Grebe-type chondrodysplasias, Brachydactyly type C, Symphalangism, Hereditary chondrodysplasia	Massague et al., 2000; Gordon and Blobe, 2008
		BMP-15	Premature ovarian failure	Gordon and Blobe, 2008
		MIS	Persistent Müllerian duct syndrome	Massague et al., 2000; Gordon and Blobe, 2008
		NODAL	Situs Ambiguus	Gordon and Blobe, 2008
		TGFβ-2,3	Cleft palate	Gordon and Blobe, 2008
	Receptor	TGFBRI	Breast cancer, Loeys-dietz, Marfan and Furlong syndromes, Familial thoracic aortic aneurysm	Rooke and Crosier, 2001; ten Dijke and Arthur, 2007; Gordon and Blobe, 2008
		BMPRII	PAH, TADD	Massague et al., 2000; Waite and Eng, 2003; ten Dijke and Arthur, 2007; Gordon and Blobe, 2008
		TGFBRII	CML, Colorectal, Gastric, Head and Neck tumours, Small cell lung cancer and Hereditary non-polyposis colorectal cancers, Loeys-dietz, Marfan and Sphrintzen-Goldberg syndromes, B and T-cell lymphoma, Retinoblastoma, Glioma, TADD	Rooke and Crosier, 2001; Gordon and Blobe, 2008
		BMPRI	Brachydactyly type A2, JPS, Bannayan-Riley-Ruvalcaba and Cowden syndrome, TADD	Waite and Eng, 2003 ; Gordon and Blobe, 2008
		ALK1	HTT2	Massague et al., 2000; Waite and Eng, 2003; ten Dijke and Arthur, 2007; Gordon and Blobe, 2008
		AMHR2	Persistent Müllerian duct syndrome	Massague et al., 2000 ; Gordon and Blobe, 2008
	Transducer/TF	Smad4	Pancreatic, Colorectal and Ovarian cancers, JPS, HHT	Massague et al., 2000; Waite and Eng, 2003; ten Dijke and Arthur, 2007; Gordon and Blobe, 2008
		Smad2	Colorectal cancer	Rooke and Crosier, 2001
		Smad3	CML	Rooke and Crosier, 2001

Pathway	Component		Disease	References
SWH	Receptor	Fat4	Breast cancer	Qi et al., 2009; Pan, 2010
	Transducer	MST 1/2	Soft tissue sarcoma	Seidel et al., 2007; Pan, 2010
		RASSF1	Lung and Kidney cancers	Kango-Singh and Singh, 2009
		NF2	NF2, Schwanomas	Evans et al., 2000; Jiang et al., 2006; Pan, 2010; Bao et al., 2011
		Lat 1/2	Breast tumours	Turenchalk et al., 1999; Zeng and Hong, 2008
	TF	YAP TAZ	Breast, Colorectal, Hepatocellular, Lung, Ovarian, Pancreatic and Prostate carcinomas	Overholtzer et al., 2006; Zender et al., 2006; Dong et al., 2007; Steinhardt et al., 2008
Toll	Receptor	TLR1	Colon cancer Gram-positive sepsis	So and Ouchi, 2010
		TLR2	Colon, Gastric and Hepatocellular carcinomas	So and Ouchi, 2010
		TLR3	Breast, Colon and Hepatocellular cancinomas, Melanoma	So and Ouchi, 2010
		TLR4	Atheroesclerosis, Arthritis, Breast, Colon, Gastric, Hepatocellular, Lung and Ovarian cancers, Carcinoma, Melanoma, Chronic inflamation	So and Ouchi, 2010; Zhu and Mohan, 2010
		TLR5	Gastric and Cervical squamous cell carcinomas	So and Ouchi, 2010
		TLR6	Hepatocellular carcinoma	So and Ouchi, 2010
		TLR7	CLL, Lupus	So and Ouchi, 2010; Zhu and Mohan, 2010
		TLR9	Breast, Cervical, Gastric, Hepatocelular and Prostate and Aquamus cell carcinomas, Glioma Diabetes type 1	So and Ouchi, 2010 ; Meyers et al. 2010
	TF	NF-KB	Diabetes type 2	Baker et al. 2011

Pathway	Component		Disease	References
Wnt	Ligand	WNT 3	Tetra-amelia	Logan and Nusse, 2004
	Receptor	LRP 5	Bone density defects, OPPG, FEVR	Logan and Nusse, 2004
		FZD 4	FEVR	Logan and Nusse, 2004
	Transducer	APC	Colon, Adeno and Basal cell carcinoma, Turcot's syndrome, FAP	Peifer and Polakis, 2000; Wechsler-Reya and Scott, 2001; Beachy et al., 2004; Logan and Nusse, 2004
		Axin	Adenocarcinoma	Beachy et al., 2004
		Axin-2	Tooth agenesis, Predisposition to Colon cancer	Logan and Nusse, 2004
		b-catenin	Adenocarcinoma	Beachy et al., 2004
	TF	TCF	Susceptibility to Diabetes type 2	Jin, 2008

Table 3. Genetic diseases associated to signalling pathways. Abbreviations: Acute lymphoblastic leukemia (ALL), Acute myeloid leukemia (AML), Chronic lymphocytic leukemia (CLL), Chronic myeloid leukemia (CML), Familial adenomatous polyposis (FAP), Familial exudative vitreoretinopathy (FEVR), Familial thoracic aortic aneurysm syndrome (TADD), Greig cephalopolysyndactyly syndrome (GCPS), Hereditary hemorrhagic telangiectasia (HHT) or Rendu-Osler-Weber syndrome, Juvenile myelomonocytic leukaemia (JMML), Juvenile polyposis syndrome (JPS), Large granular lymphocyte leukemia (LGL), Myeloproliferative diseases (MPDs), Osteoperosis-pseudoglioma syndrome (OPPG), Primary pulmonary arterial hypertension (PAH), Postaxial polydactyly type A (PAP-A), Pallister–Hall syndrome (PHS), Polycythemia vera (PV), Severed combined immunodeficiency (SCID).

4. Drosophila as a model organism to analyse the genetic and cellular biology of signalling

Because of the prominent roles that signalling plays during development, and its relevance in maintaining adult homeostasis and normal physiology (see Table 3), the analysis and experimental manipulation of signalling pathways has a central role in biomedical research. In this context, a key aspect in the analysis of signalling is the use of experimental systems allowing the identification of novel components of the different pathways, the manipulation of their activity by genetic and pharmacological approaches and the understanding of the mechanisms by which they regulate cell behaviour. Not surprisingly, the organisms that most have contributed to the analysis of signalling are those allowing a robust and efficient genetic approach to unravel gene function, in particular *Caenorhabditis elegans* and *Drosophila melanogaster*. In fact, many known components of all signalling pathway were identified in these organisms through genetic screens. The rationale of these experiments is straightforward: mutations affecting the same signalling pathway result in a similar phenotype and in general display genetic interactions. Thus, exhaustive genetic screens aimed to identify

genes regulating embryonic segmentation in flies were instrumental to identify many components of the Notch, BMP, Hh and Wnt pathways (Nusslein-Volhard and Wieschaus, 1980), and genetic screens carried out in sensitized genetic backgrounds resulted in the identification of additional components of these pathways and also of the EGFR and InR pathways (Greaves et al., 1999; Rebay et al., 2000; Huang and Rubin, 2000; Guichard et al., 2002; Mahoney et al., 2006). More recently, mosaic screens in adult structures of the fly uncovered the SWH pathway, because of its contribution to the regulation of cell proliferation, competition and apoptosis (Cho et al., 2006; Harvey and Tapon, 2007 Tyler et al., 2007).

Signalling in *C. elegans* and *D. melanogaster* has been analysed in many different developmental settings, including the formation of the gonads (Horvitz and Sternberg, 1991), the development of the imaginal discs (Sotillos and de Celis, 2005; de Celis, 2003) and the patterning of the embryonic segments (Irish and Gelbart, 1987; Wesley, 1999), among many others. In general these studies rely in a good cellular description of the tissue and its development, the possibility of directly monitoring the domains of signalling using specific reporter assays, and the availability of sophisticated techniques to manipulate the activity of any pathway component and analyse its phenotypic consequences. We will describe in what follows and from the perspective of signalling some relevant aspects of the development of the Drosophila wing imaginal disc, one experimental system that has been instrumental in the analysis of cell signalling during the development of epithelial tissues.

5. The wing imaginal disc of Drosophila as a developmental model to analyse the structure, interactions and biological outcomes of signalling pathways

Imaginal discs are epithelial structures that give rise to most of the adult external structures of the fly. The wing imaginal disc starts its development as a group of about 20 embryonic ectodermal cells (Cohen et al., 1993). These cells proliferate during larval development to form the mature third instar disc, composed by approximately 50000 cells primed to differentiate during metamorphosis the fly wing and part of the thorax (Figure 3) (de Celis, 2003). Cell signalling pervades the development of the wing imaginal disc; from the initial step of primordium specification to the last stages of cellular differentiation. In this manner, the cells that constitute the wing disc primordium are determined by the combined actions of the BMP, EGFR and Wnt signalling pathways, which regulate the expression of the transcription factors specifying the group of wing disc precursor cells (Cohen et al., 1993; Goto and Hayashi, 1997). From this point onwards, the primordium enters a developmental program that involves cell division and different stages of territorial organization by which all cells acquire their individual genetic specification (Zecca and Struhl, 2002).

Territorial subdivisions in the wing disc are regulated by coordinate signalling events involving the EGFR, BMP, Notch, Hh and Wnt pathways (Figure 3). First, the wing primordium is subdivided into anterior and posterior compartments, which correspond to independent cell lineages of polyclonal origin. The posterior compartment is the source of the ligand Hh, which signalling contributes to the maintenance of the anterior-posterior compartment boundary and sets specific domains of gene expression in anterior cells from this early stage onwards (Tabata and Kornberg, 1994) (Figure 3). The subdivision into anterior-posterior compartments is followed later in development by patterning along the proximo-distal axes of the disc, a process that relies in the establishment of complementary domains of signalling by the EGFR pathway in proximal cells and by the Wnt pathway in distal cells (Zecca and Struhl, 2002). These two complementary signalling centers determine the expression of transcription factors such as Apterous, the Iroquois gene complex and Spalt in proximal cells, defining what will become the thorax of the mature wing disc (Cavodeassi et

al., 2002). The establishment of the domain of *apterous* expression also triggers the initiation of the wing region, which will appear centred along the boundary between *apterous* expressing cells, the future dorsal compartment, and *apterous* non-expressing cells, corresponding to the ventral compartment. This boundary corresponds to the future dorso-ventral compartment boundary of the wing, and is the place where Notch signalling is activated to regulate the expression of the co-factor Vestigial, which labels the primordium of the wing blade (Figure 3). The establishment of the wing blade territory as a domain of cells expressing vestigial along the dorso-ventral boundary also requires *wingless* function, which expression in distal cells is also regulated by the transcription factors defining the proximo-distal axes of the wing disc (Wu and Cohen, 2002; Whitworth and Russell, 2003; Zirin and Mann, 2007). At this stage, which corresponds to the second instar larvae, the wing disc already contains the future thorax and wing territories, and the wing is already subdivided into anterior-posterior and dorso-ventral compartments. The subsequent development of the wing disc epithelium involves the generation of the wing hinge, originated in the proximal part of the wing blade and specified by two novel rings of *wingless* expression (Perea et al., 2009), and the establishment of smaller domains of expression in both the thorax and wing regions (Figure 3).
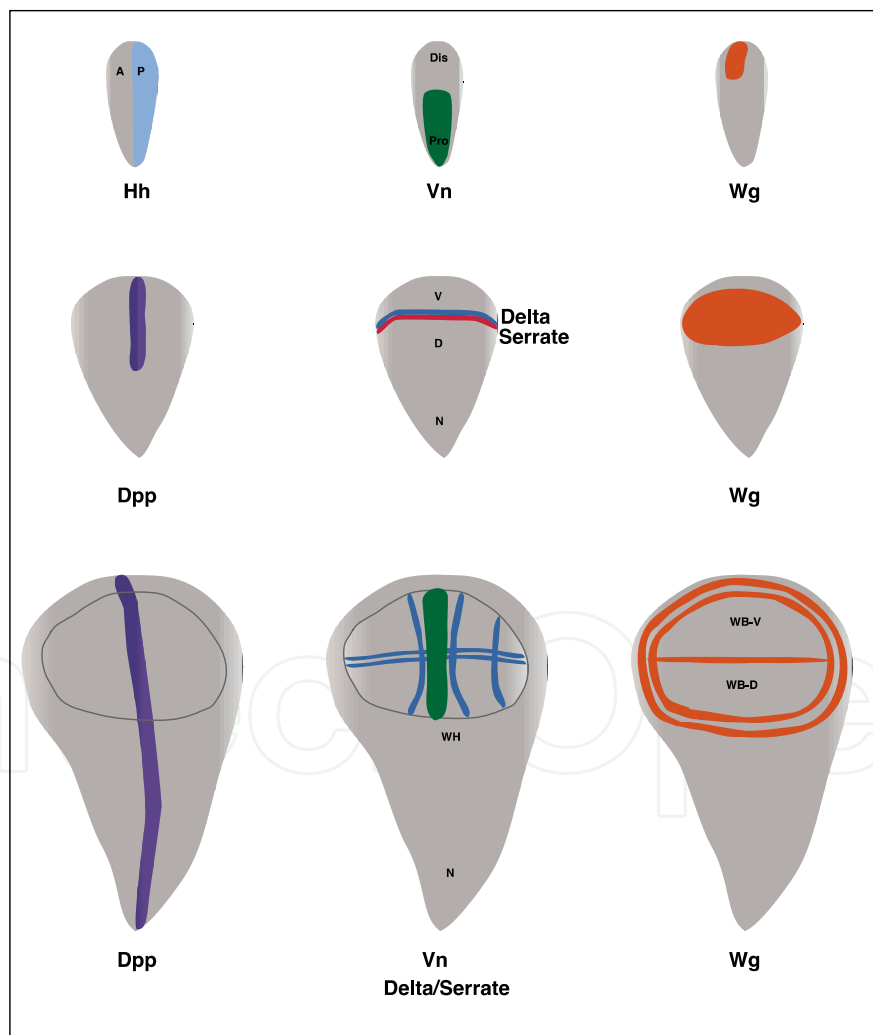
Fig. 3. Schematic representation of the wing disc during the second (upper panels), mid-third (middle panel) and late-third (bottom panel) larval instard, showing the expression of ligands in coloured stripes.

The global subdivision of the wing disc into large territories described above is followed by the regional specification of the pattern elements characteristic of the wing and thorax. These elements, the sensory organs decorating the thorax and wing margin and the longitudinal veins running along the proximo-distal length of the wing blade and hinge, differentiate from fields of competent cells, the proneural clusters and the provein territories, respectively. As it happened with the earlier territorial subdivisions, the positioning of each proneural cluster and provein territory also relies on the function of different signalling pathways, mainly the Wnt, Hh and BMP pathways for the proneural clusters and the BMP and Hh pathways for the proveins (Tomoyasu et al., 1998; Sato et al., 1999; de Celis et al., 1999; Cavodeassi et al., 2001; de Celis, 2003). These pathways now regulate the expression of several transcription factors that control the expression of the proneural and provein genes, constituting a landscape of transcriptional regulators that has been named the "pre-pattern" (Stern, 1954; Cavodeassi et al., 2001). At this stage, all patterned elements are genetically specified in the form of groups of cells with a competence to differentiate individual cell types. The last stage before cell differentiation is the assignation of cell fates within proneural clusters and provein territories. This process relies in a complex set of cell interactions mediated by the Notch and EGFR pathways and generally named "lateral inhibition". During lateral inhibition, the EGFR pathway promotes the acquisition of the sensory organ precursor and vein fates and the Notch pathway prevents other competent cells from following these fates. In this manner, the end result is that only one cell from the proneural clusters will acquire the sensory organ precursor fate and enter a particular pattern of cell divisions (Pi and Chien, 2007). A similar process operates in the provein fields using the same two pathways, but in this case the maintenance of stripes of cells ready to differentiate as veins during pupal development also requires the activity of the BMP pathway, which ligand becomes expressed at this stage in the developing veins (de Celis, 2003).

The patterning of the disc is accompanied by a continuous increase in its size (Baker, 2007). Wing disc growth occurs mainly by cell proliferation, with cells taking about 10 hours to go through the cell cycle (González Gaitán et al., 1994; Milan et al., 1996; Neufeld et al., 1998). Several pathways such as the EGFR, Wnt, SWH, Notch and TGFβ play key roles in promoting cell division. In this manner, a reduction (EGFR, Wnt, Notch and TGFβ) or increase (SWH) in the activity of these pathways results in the formation of smaller adult structures, and this reduction in size is caused by the generation of a lower than normal number of cells (see Figure 4). Interestingly, these effects have a strong component of territorial specificity, because the reduction of each pathway activity affects each territory of the wing disc to different extents. For example, the Wnt pathway is particularly required to promote cell proliferation in the wing hinge (Dichtel-Danjoy et al., 2009), whereas the Notch pathway is mostly required in the wing blade (de Celis and Garcia-Bellido, 1994). As mutations affecting the activity of the EGFR, Wnt, BMP and Notch pathways also affect territorial specification, the defects in cell proliferation are accompanied by changes in the general organization of the disc and its patterning. Cell division is coupled with cell growth in a manner that wing disc cells maintain a similar size during their proliferative phase. From the perspective of cellular growth, the most relevant pathway operating in the wing disc is the InR/Tor signalling system (Hietakangas and Cohen, 2009). The activity of InR/Tor is mostly required as a sensor to translate nutritional and humoral signals into
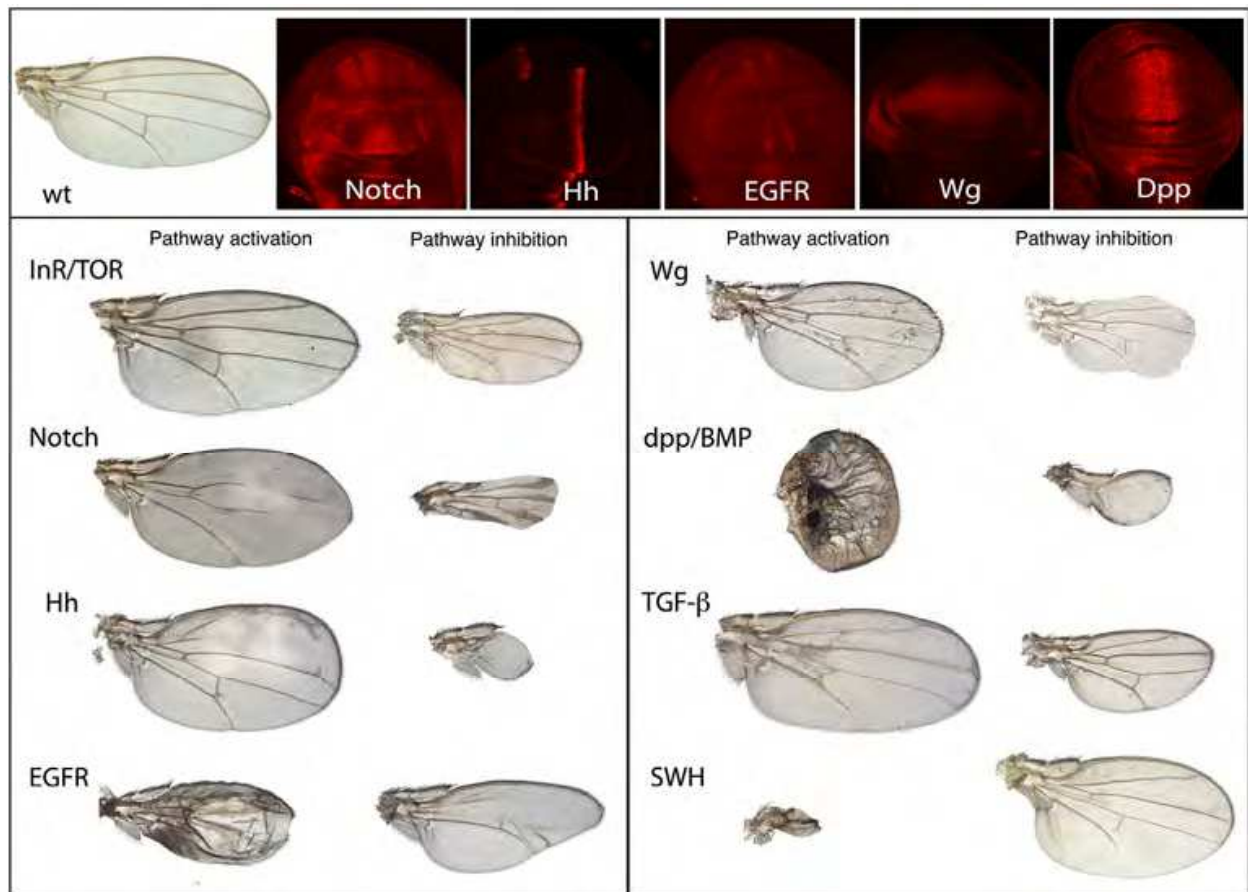
Fig. 4. Upper panel: Pictures of a wild type wing (wt, left) and third instar imaginal discs showing the domains of Notch, Hh, EGFR, Wg and Dpp signalling. Bottom panel: Pictures of mutant wings in which the activity of the InR/Tor, Notch, Hh and EGFR (left two columns), and Wg, dpp/BMP, TGF-β and SWH (right two columns) is either increased (Pathway activation columns) or decreased (Pathway inhibition columns)

adequate rates of protein synthesis, but also provides survival signals for the cell and stimulates cell division (Hietakangas and Cohen, 2009). In general, mutations reducing InR/Tor signalling result in the formation of adult structures smaller than normal, due to both a reduction in cell size and a diminution in the number of cells (see Figure 4).

Although the wing disc is probably one of the best understood biological systems, there are still many caveats regarding the molecular mechanisms that drive cell division during the growth of the disc. Similarly, it is not entirely understood how the progress through the cell cycle is coordinated with cellular growth, and what makes the disc stop its proliferative phase when it reaches a particular size. In this manner, the molecular mechanisms ensuring the formation of patterned structures of the appropriate dimensions are still elusive. Despite of this, the current knowledge about imaginal disc development is robust enough to use this system as a model to unravel the intricacies and roles played by signalling pathways during development, and to model human diseases, using the advantages of fly genetics. There are two key aspects of the analysis of signalling in the wing disc that favours this system as an experimental model. First is the facility by which mutant phenotypes can be assigned to specific failures in particular signalling pathways. This simplifies the identification of

additional components of each signalling pathway by the phenotype caused by mutations in the corresponding genes (Figure 4), and also allows the design of genetic screens aimed to identify novel elements of the pathway. Secondly, the spatial and temporal domains of signalling can be precisely described by monitoring the expression of target genes in the disc, and this allows the visualization of receptor activity both in normal conditions and under experimental manipulations (Figure 4).

6. Genetic approaches to identify additional components of signalling pathways

Some of the main reasons to choose Drosophila for the study of signalling are the availability of sophisticated genetic techniques to manipulate gene activity and the knowledge of the Drosophila genome (Adams et al., 2000; Matthews et al., 2005). First, there is a strong conservation between Drosophila proteins involved in signalling pathways and their human counterparts (Reiter et al., 2001; Chien et al., 2002 see Table 1). Second, Drosophila genes involved in signalling are generally represented in single copies, reducing the possibility of redundancy and facilitating the characterization of gene functions (Adams et al., 2000). Third, loss- and gain-of-function conditions in genes coding for signalling proteins of all pathways usually result in complementary phenotypes, allowing the assignation of genes to pathways based on mutant phenotypes (Molnar et al., 2006; Cruz et al., 2009 see Figure 4). The phenotypes observed upon hyper-activation of the pathways also allow the design of gain-of-function screens, which have the potential to uncover genes not found in loss-of-function screens due to functional redundancy (Rorth et al., 1998). Finally, mutations in different elements of each signalling pathway generally display gene-dose dependent phenotypic interactions in genetic combinations, allowing the hierarchical ordering of pathway components through genetic analysis.

There are two main ways in which genetic screens have been used to identify the components of different signalling pathways. In a first approach, newly induced mutants are tested for a phenotype in a particular structure which development depends on the normal activity of specific signalling pathways. In these cases, the mutants can be induced by chemical mutagenesis or by mobilizing transposable elements, and they can be analyzed either in homozigosity in the entire animal, or in mosaics in adult tissues using a combination of the Gal4/UAS and FRT/FLP systems. A recent example of this approach is the search for novel components of the Notch signalling pathway, in which a large collection of interference RNAs is expressed in the wing disc to systematically reduce the expression of the endogenous genes, resulting in the identification of Notch pathway candidates based on the resulting mutant phenotypes (Mummery-Widmer et al., 2009). In addition, whereas chemical mutagenesis and the expression of interference RNA result in loss of gene function, the use of transposable elements with UAS sequences allows the generation of gain-of-function conditions, which can be restricted to the tissue of interest (Rorth et al., 1998). Complementary to these approaches, the search for novel components of signalling pathways has also relied in the design of "modifier" screens, in which both loss- and gain-of-function mutants are tested in particular mutant backgrounds. In these cases, the screen aims to identify genes belonging to a pre-determined set of interacting genes. Some examples of successful screens aiming to identify members of known signalling pathways are those targeting the Sevenless and EGFR (Karim et al., 1996; Huang and Rubin, 2000; Taguchi et al., 2000; Rebay et al., 2000), Notch (Verheyen et al., 1996; Go and Artavanis-

Tsakonas, 1998; Muller et al., 2005a), Dpp (Raftery et al., 1995; Chen et al., 1998; Su et al., 2001), JAK/STAT (Bach et al., 2003; Mukherjee et al., 2006), Hh (Haines and van den Heuvel, 2000; Collins and Cohen, 2005), TNF (Geuking et al., 2005) and Wnt (Greaves et al., 1999; Cox et al., 2000; Desbordes et al., 2005) pathways.

Although the use of genetic screens in vivo has many advantages, they are time-consuming and difficult to escalate genome-wide. For these reasons, and based on the knowledge of the Drosophila genome, several techniques using Drosophila cells in culture and interference RNA have been adopted in the search for novel signalling components. These screens allow the identification of genes affecting the expression of reporter constructs that reveal the activity of specific signalling pathways (Clemens et al., 2000; Flockhart et al., 2006). This approach has been used to search for novel components of the Hh (Lum et al., 2003; Nybakken et al., 2005), and of the Wnt (DasGupta et al., 2005), JAK/Stat (Muller et al., 2005b), TNF (Kleino et al., 2005), Tor (Lindquist et al., 2011) and ERK (Friedman and Perrimon, 2006) signalling pathways.

7. Drosophila models of genetic diseases

It is clear that the main advantage of the Drosophila model from a biomedical perspective is the possibility of designing genetic screens aimed to the identification of genes involved in a particular phenotypic outcome. In this context, it is worth noticing that an estimated 60% of genes related to human diseases have orthologs in Drosophila, and this category includes all genes involved in cell signalling (Chien et al., 2002; Reiter et al., 2001). The possibility of generating transgenic flies expressing modified non-Drosophila proteins is allowing the design of "humanized" fly models for a variety of human genetic diseases such as Multiple Endocrine Neoplasia Type 2 (Read et al., 2005), cardiomyopathies (Vu Manh et al., 2005) and Adenomatous Polyposis Coli (APC; Bhandari and Shashidhara, 2001) and several neurodegenerative diseases (Fernandez-Funez et al., 2000; Crowther et al., 2004; Sang and Jackson, 2005; Botas, 2007; Branco et al., 2008; Cukier et al., 2008; Miller et al., 2010). The aim of these experiments is to recreate in a fly tissue some of the cellular aspects of the pathology caused by the human protein, and to use this genetic background as a platform to search for genes affecting the phenotype caused by the miss-expression of this protein (Botas, 2007). In the long term, it is expected that the identification of additional genes involved in a particular phenotypic outcome will allow the search for chemotherapeutic agents with therapeutical value. In addition to genetic searches, Drosophila also permits to recapitulate the biology of particular diseases in vivo systems, an approach that is been applied to the study of tumorigenesis using among other tissues the imaginal discs (Janic et al., 2010). In this manner Drosophila tissues can be used not only to track down the steps leading to tumour initiation, progression and metastasis in vivo, but also to manipulate in genetic mosaics the activity of genes leading to tumoral growth and to assay therapeutic drugs (Kango-Singh and Halder, 2004; Vidal and Cagan, 2006; Jang et al., 2007; Januschke and Gonzalez, 2008; Read et al., 2009; Caldeira et al., 2009; Das and Cagan, 2010; Bina et al., 2010; Wu et al., 2010). This approach is contributing to dissect the effects of tumour-promoting and tumour-suppressing genes in the regulation of proliferation, apoptosis, cell-adhesion, trafficking and cell polarity, and revealed the importance of cellular interactions in the outcome of tumoral progression. Finally, the modelling of specific cancers, such as type 2 multiple endocrine neoplasia (MEN2, caused by hyper-activation of RET; Read et al., 2005b) has allowed the design and use of pharmacological approaches to modify the phenotype

caused by oncogenic forms of dRET (Das and Cagan, 2010). In addition, a similar approach prove successful in interfering with the activation of the EGFR (Aritakula and Ramasamy, 2008), suggesting that *Drosophila* has also the potential to be a robust model system for the screening of anticancer drugs in vivo.

8. Acknowledgements

9. References

Adams, M. D. Celniker, S. E. Holt, R. A. Evans, C. A. Gocayne, J. D. Amanatides, P. G. Scherer, S. E. Li, P. W. Hoskins, R. A. Galle, R. F. et al. (2000). The genome sequence of Drosophila melanogaster. *Science* 287, 2185-95.

Akimaru, H., Chen, Y., Dai, P., Hou, D. X., Nonaka, M., Smolik, S. M., Armstrong, S., Goodman, R. H. and Ishii, S. (1997a). Drosophila CBP is a co-activator of cubitus interruptus in hedgehog signalling. *Nature* 386, 735-8.

Akimaru, H., Hou, D. X. and Ishii, S. (1997b). Drosophila CBP is required for dorsal-dependent twist gene expression. *Nat Genet* 17, 211-4.

Angers, S. and Moon, R. T. (2009). Proximal events in Wnt signal transduction. *Nat Rev Mol Cell Biol* 10, 468-77.

Aoki, Y.,Nihori,T, Kawame, H., Kurosawa, K., Ohashi, H., Tanaka, Y., Filocamo, M., Kato, K., Suzuki, Y., Kure, S. et al. (2005). Germline mutations in HRAS proto-oncogene cause Costello syndrome. *Nat Genet* 37, 1038-40.

Araujo, H., Negreiros, E. and Bier, E. (2003). Integrins modulate Sog activity in the Drosophila wing. *Development* 130, 3851-64.

Arbouzova, N. I. and Zeidler, M. P. (2006). JAK/STAT signalling in Drosophila: insights into conserved regulatory and cellular functions. *Development* 133, 2605-16.

Aritakula, A. and Ramasamy, A. (2008). Drosophila-based in vivo assay for the validation of inhibitors of the epidermal growth factor receptor/Ras pathway. *J. Biosci.* 33, 731-742.

Arnold, S. J. and Robertson, E. J. (2009). Making a commitment: cell lineage allocation and axis patterning in the early mouse embryo. *Nat Rev Mol Cell Biol* 10, 91-103.

Arnone, M. I. and Davidson, E. H. (1997). The hardwiring of development: organization and function of genomic regulatory systems. *Development* 124, 1851-64.

Avraham, R. and Yarden, Y. (2011). Feedback regulation of EGFR signalling: decision making by early and delayed loops. *Nat Rev Mol Cell Biol* 12, 104-17.

Axelrod, J. D. (2010). Delivering the lateral inhibition punchline: it's all about the timing. *Sci Signal* 3, pe38.

Bach, E. A., Vincent, S., Zeidler, M. P. and Perrimon, N. (2003). A Sensitized Genetic Screen to Identify Novel Regulators and Components of the Drosophila Janus Kinase/Signal Transducer and Activator of Transcription Pathway. *Genetics* 165, 1149-1166.

Bachmann, A. and Knust, E. (1998). Dissection of cis-regulatory elements of the Drosophila gene Serrate. *Dev. Genes Evol.* 208, 346-351.

Baeg, G.-H., Lin, X., Khare, N., Baumgartner, S. and Perrimon, N. (2001). Heparan sulfate proteoglycans are critical for the organization of the extracellular distribution of Wingless. *Development* 128, 87-94.

Baker, N. E. (2007). Patterning signals and proliferation in Drosophila imaginal discs. *Curr Opin Genet Dev* 17, 287-93.

Baker, R. G., Hayden, M. S. and Ghosh, S. (2011). NF-kappaB, inflammation, and metabolic disease. *Cell Metab* 13, 11-22.

Baonza, A., Murawsky, C. M., Travers, A. A. and Freeman, M. (2002). Pointed and Tramtrack69 establish an EGFR-dependent transcriptional switch to regulate mitosis. *Nat Cell Biol* 4, 976-980.

Bartscherer, K. and Boutros, M. (2008). Regulation of Wnt protein secretion and its role in gradient formation. *EMBO Rep* 9, 977-82.

Bao, Y., Hata, Y., Ikeda, M. and Withanage, K. (2011). Mammalian Hippo pathway: from development to cancer and beyond. *J Biochem* 149, 361-79.

Barker, N., Hurlstone, A., Musisi, H., Miles, A., Bienz, M. and Clevers, H. (2001). The chromatin remodelling factor Brg-1 interacts with beta-catenin to promote target gene activation. *EMBO J* 20, 4935-43.

Barrio, R., Lopez-Varea, A., Casado, M. and de Celis, J. F. (2007). Characterization of dSnoN and its relationship to Decapentaplegic signalling in Drosophila. *Dev Biol* 306, 66-81.

Beachy, P. A., Karhadkar, S. S. and Berman, D. M. (2004). Tissue repair and stem cell renewal in carcinogenesis. *Nature* 432, 324-31.

Bentires-Alj, M., Kontaridis, M. I. and Neel, B. G. (2006). Stops along the RAS pathway in human genetic disease. *Nat Med* 12, 283-5.

Bernard, F., Krejci, A., Housden, B., Adryan, B. and Bray, S. J. (2010). Specificity of Notch pathway activation: twist controls the transcriptional output in adult muscle progenitors. *Development* 137, 2633-42.

Bethani, I., Skanland, S. S., Dikic, I. and Acker-Palmer, A. (2010). Spatial organization of transmembrane receptor signalling. *EMBO J* 29, 2677-88.

Bhandari, P. and Shashidhara, L. S. (2001). Studies on human colon cancer gene APC by targeted expression in Drosophila. *Oncogene* 20, 6871-80.

Bina, S., Wright, V. M., Fisher, K. H., Milo, M. and Zeidler, M. P. (2010). Transcriptional targets of Drosophila JAK/STAT pathway signalling as effectors of haematopoietic tumour formation. *EMBO Rep* 11, 201-7.

Blair, E., Redwood, C., Ashrafian, H., Oliveira, M., Broxholme, J., Kerr, B., Salmon, A., Ostman-Smith, I. and Watkins, H. (2001). Mutations in the gamma(2) subunit of AMP-activated protein kinase cause familial hypertrophic cardiomyopathy: evidence for the central role of energy compromise in disease pathogenesis. *Hum Mol Genet* 10, 1215-20.

Bonn, S. and Furlong, E. E. (2008). cis-Regulatory networks during development: a view of Drosophila. *Curr Opin Genet Dev* 18, 513-20.

Bos, J. L. (1989). ras oncogenes in human cancer: a review. *Cancer Res* 49, 4682-9.

Botas, J. (2007). Drosophila researchers focus on human disease. *Nat Genet* 39, 589-91.

Branco, J., Al-Ramahi, I., Ukani, L., Perez, A. M., Fernandez-Funez, P., Rincon-Limas, D. and Botas, J. (2008). Comparative analysis of genetic modifiers in Drosophila points to common and distinct mechanisms of pathogenesis among polyglutamine diseases. *Hum Mol Genet* 17, 376-90.

Bray, S. J. (2006). Notch signalling: a simple pathway becomes complex. *Nat Rev Mol Cell Biol* 7, 678-89.

Brogiolo, W., Stocker, H., Ikeya, T., Rintelen, F., Fernandez, R. and Hafen, E. (2001). An evolutionarily conserved function of the Drosophila insulin receptor and insulin-like peptides in growth control. *Curr Biol* 11, 213-21.

Bromberg, J. (2002). Stat proteins and oncogenesis. *J Clin Invest* 109, 1139-42.

Caldeira, J., Pereira, P. S., Suriano, G. and Casares, F. (2009). Using fruitflies to help understand the molecular mechanisms of human hereditary diffuse gastric cancer. *Int J Dev Biol* 53, 1557-61.

Campisi, J. and d'Adda, F. (2007). Cellular senescence: when bad things happen to good cells. *Nature Reviews Molecular Cell Biology* 8, 729-740.

Carmena, A., Gisselbrecht, S., Harrison, J., Jimenez, F. and Michelson, A. M. (1998). Combinatorial signalling codes for the progressive determination of cell fates in the Drosophila embryonic mesoderm. *Genes Dev* 12, 3910-22.

Carbone, D. P. (2000). Chromosome 19 translocation, overexpression of Notch3, and human lung cancer. *J Natl Cancer Inst* 92, 1355-7.

Cavodeassi, F., Modolell, J. and Gomez-Skarmeta, J. L. (2001). The Iroquois family of genes: from body building to neural patterning. *Development* 128, 2847-55.

Cavodeassi, F., Rodriguez, I. and Modolell, J. (2002). Dpp signalling is a key effector of the wing-body wall subdivision of the Drosophila mesothorax. *Development* 129, 3815-3823.

Chen, Y., Riese, M. J., Killinger, M. A. and Hoffmann, F. M. (1998). A genetic screen for modifiers of Drosophila decapentaplegic signalling identifies mutations in punt, Mothers against dpp and the BMP-7 homologue, 60A. *Development* 125, 1759-1768.

Chen, Y., Goodman, R. H. and Smolik, S. M. (2000). Cubitus interruptus requires Drosophila CREB-binding protein to activate wingless expression in the Drosophila embryo. *Mol Cell Biol* 20, 1616-25.

Chen, Y. and Struhl, G. (1996). Dual roles for Patched in sequestering and transducing Hedgehog. *Cell* 87, 553-563.

Chien, S., Reiter, L. T., Bier, E. and Gribskov, M. (2002). Homophila: human disease gene cognates in Drosophila. *Nucleic Acids Res* 30, 149-51.

Chien, A. J., Conrad, W. H. and Moon, R. T. (2009). A Wnt survival guide: from flies to human disease. *J Invest Dermatol* 129, 1614-27.

Cho, E., Feng, Y., Rauskolb, C., Maitra, S., Fehon, R. and Irvine, K. D. (2006). Delineation of a Fat tumor suppressor pathway. *Nat Genet* 38, 1142-50.

Chopra, V. S. and Levine, M. (2009). Combinatorial patterning mechanisms in the Drosophila embryo. *Brief Funct Genomic Proteomic* 8, 243-9.

Clemens, J. C., Worby, C. A., Simonson-Leff, N., Muda, M., Maehama, T., Hemmings, B. A. and Dixon, J. E. (2000). Use of double-stranded RNA interference in Drosophila cell lines to dissect signal transduction pathways. *P.N.A.S.* 97, 6499-6503.

Cohen, B., Simcox, A. A. and Cohen, S. M. (1993). Allocation of the thoracic imaginal primordia in the Drosophila embryo. *Development* 117, 397-608.

Collins, R. T. and Cohen, S. M. (2005). A Genetic Screen in Drosophila for Identifying Novel Components of the Hedgehog Signalling Pathway. *Genetics* 170, 173-184.

Constantinescu, S. N., Girardot, M. and Pecquet, C. (2008). Mining for JAK-STAT mutations in cancer. *Trends Biochem Sci* 33, 122-31.

Cox, R. T., McEwen, D. G., Myster, D. L., Duronio, R. J., Loureiro, J. and Peifer, M. (2000). A screen for mutations that suppress the phenotype of Drosophila armadillo, the beta-catenin homolog. *Genetics* 155, 1725-40.

Crowther, D. C., Kinghorn, K. J., Page, R. and Lomas, D. A. (2004). Therapeutic targets from a Drosophila model of Alzheimer's disease. *Curr Opin Pharmacol* 4, 513-6.

Cruz, C., Glavic, A., Casado, M. and de Celis, J. F. (2009). A gain-of-function screen identifying genes required for growth and pattern formation of the Drosophila melanogaster wing. *Genetics* 183, 1005-26.

Cukier, H. N., Perez, A. M., Collins, A. L., Zhou, Z., Zoghbi, H. Y. and Botas, J. (2008). Genetic modifiers of MeCP2 function in Drosophila. *PLoS Genet* 4, e1000179.

Dai, H., Hogan, C., Gopalakrishnan, B., Torres-Vazquez, J., Nguyen, M., Park, S., Raftery, L. A., Warrior, R. and Arora, K. (2000). The zinc finger protein schnurri acts as a Smad partner in mediating the transcriptional response to decapentaplegic. *Dev Biol* 227, 373-87.

Dang, T. P., Gazdar, A. F., Virmani, A. K., Sepetavec, T., Hande, K. R., Minna, J. D., Roberts, J. R. ,

Dong, J., Feldmann, G., Huang, J., Wu, S., Zhang, N., Comerford, S. A., Gayyed, M. F., Anders, R. A., Maitra, A. and Pan, D. (2007). Elucidation of a universal size-control mechanism in Drosophila and mammals. *Cell* 130, 1120-33.

Das, T. and Cagan, R. (2010). Drosophila as a novel therapeutic discovery tool for thyroid cancer. *Thyroid* 20, 689-95.

DasGupta, R., Kaykas, A., Moon, R. T. and Perrimon, N. (2005). Functional genomic analysis of the Wnt-wingless signalling pathway. *Science* 308, 826-33.

de Celis, J. F. (2003). Pattern formation in the Drosophila wing: the development of the veins. *BioEssays* 25, 443-451.

de Celis, J. F., Barrio, R. and Kafatos, F. C. (1999). Regulation of the spalt/spalt-related gene complex and its function during sensory organ development in the Drosophila thorax. *Development* 126, 2653-2662.

de Celis, J. F. and Garcia-Bellido, A. (1994). Roles of the Notch gene in Drosophila wing morphogenesis. *Mech. Dev.*, 109-122.

Desbordes, S. C., Chandraratna, D. and Sanson, B. (2005). A Screen for Genes Regulating the Wingless Gradient in Drosophila Embryos. *Genetics* 170, 749-766.

Dichtel-Danjoy, M. L., Caldeira, J. and Casares, F. (2009). SoxF is part of a novel negative-feedback loop in the wingless pathway that controls proliferation in the Drosophila wing disc. *Development* 136, 761-9.

Downward, J. (2003). Targeting RAS signalling pathways in cancer therapy. *Nat Rev Cancer* 3, 11-22.

Duboc, V. and Logan, M. P. (2009). Building limb morphology through integration of signalling modules. *Curr Opin Genet Dev* 19, 497-503.

Dubnicoff, T., Valentine, S. A., Chen, G., Shi, T., Lengyel, J. A., Paroush, Z. and Courey, A. J. (1997). Conversion of dorsal from an activator to a repressor by the global corepressor Groucho. *Genes Dev* 11, 2952-7.

Ellisen, L. W., Bird, J., West, D. C., Soreng, A. L., Reynolds, T. C., Smith, S. D. and Sklar, J. (1991). TAN-1, the human homolog of the Drosophila notch gene, is broken by chromosomal translocations in T lymphoblastic neoplasms. *Cell* 66, 649-61.

Evans, D. G., Sainio, M. and Baser, M. E. (2000). Neurofibromatosis type 2. *J Med Genet* 37, 897-904.

Feng, X. H., Zhang, Y., Wu, R. Y. and Derynck, R. (1998). The tumor suppressor Smad4/DPC4 and transcriptional adaptor CBP/p300 are coactivators for smad3 in TGF-beta-induced transcriptional activation. *Genes Dev* 12, 2153-63.

Fernandez, B. G., Arias, A. M. and Jacinto, A. (2007). Dpp signalling orchestrates dorsal closure by regulating cell shape changes both in the amnioserosa and in the epidermis. *Mech Dev* 124, 884-97.

Fernandez-Funez, P., Nino-Rosales, M. L., de Gouyon, B., She, W. C., Luchak, J. M., Martinez, P., Turiegano, E., Benito, J., Capovilla, M., Skinner, P. J. et al. (2000). Identification of genes that modify ataxin-1-induced neurodegeneration. *Nature* 408, 101-6.

Flockhart, I., Booker, M., Kiger, A., Boutros, M., Armknecht, S., Ramadan, N., Richardson, C., Xu, T., Perrimon, N. and Mathey-Prevot, B. (2006). FlyRNAi: the Drosophila RNAi screening center database *Nucleic Acids Research* 34, 489-494.

Friedman, A. and Perrimon, N. (2006). A functional RNAi screen for regulators of receptor tyrosine kinase and ERK signalling. *Nature* 444, 230-4.

Funakoshi, Y., Minami, M. and Tabata, T. (2001). mtv shapes the activity gradient of the Dpp morphogen through regulation of thickveins. *Development* 128, 67-74.

Gerondakis, S., Grumont, R., Gugasyan, R., Wong, L., Isomura, I., Ho, W. and Banerjee, A. (2006). Unravelling the complexities of the NF-kappaB signalling pathway using mouse knockout and transgenic models. *Oncogene* 25, 6781-99.

Geuking, P., Narasimamurthy, R. and Basler, K. (2005). A Genetic Screen Targeting the Tumor Necrosis Factor/Eiger Signalling Pathway: Identification of Drosophila TAB2 as a Functionally Conserved Component. *Genetics* 171, 1683-1694.

Gilbert, M. M., Beam, C. K., Robinson, B. S. and Moberg, K. H. (2009). Genetic interactions between the Drosophila tumor suppressor gene ept and the stat92E transcription factor. *PLoS One* 4, e7083.

Go, M. J. and Artavanis-Tsakonas, S. (1998). A genetic screen for novel components of the Notch signalling pathway during Drosophila bristle development. *Genetics* 150, 211-220.

González Gaitán, M., Capdevila, M. P. and García Bellido, A. (1994). Cell proliferation patterns in the wing imaginal disc of Drosophila. *Mech. Dev.* 46, 183-200.

Gordon, K. J. and Blobe, G. C. (2008). Role of transforming growth factor-beta superfamily signalling pathways in human disease. *Biochim Biophys Acta* 1782, 197-228.

Goto, S. and Hayashi, S. (1997). Specification of the embryonic limb primordium by graded activity of Decapentaplegic. *Development* 124, 125-132.

Greaves, S., Sanson, B., White, P. and Vincent, J. P. (1999). A screen for identifying genes interacting with armadillo, the Drosophila homolog of beta-catenin. *Genetics* 153, 1753-66.

Greer, E. L. and Brunet, A. (2008). FOXO transcription factors in ageing and cancer. *Acta Physiol (Oxf)* 192, 19-28.

Grusche, F. A., Richardson, H. E. and Harvey, K. F. (2010). Upstream regulation of the hippo size control pathway. *Curr Biol* 20, R574-82.

Guichard, A., Srinivasan, S., Zimm, G. and Bier, E. (2002). A screen for dominant mutations applied to components in the Drosophila EGF-R pathway. *Proc Natl Acad Sci U S A* 99, 3752-7.

Haber, D. A. (2006). Transforming properties of YAP, a candidate oncogene on the chromosome 11q22 amplicon. *Proc Natl Acad Sci U S A* 103, 12405-10.

Haenlin, M., Kramatschek, B. and Campos-Ortega, J. A. (1990). The pattern of transcription of the neurogenic gene Delta of Drosophila melanogaster. *Development* 110, 905-914.

Haenlin, M., Kunisch, M., Kramatschek, B. and Campos-Ortega, J. A. (1994). Genomic regions regulating early embryonic expression of the Drosophila neurogenic gene Delta. *Mech. Dev.* 47, 99-110.

Haines, N. and van den Heuvel, M. (2000). A Directed Mutagenesis Screen in Drosophila melanogaster Reveals New Mutants That Influence hedgehog Signalling. *Genetics* 156, 1777-1785.

Halder, G. and Johnson, R. L. (2011). Hippo signalling: growth control and beyond. *Development* 138, 9-22.

Harper, J. A., Yuan, J. S., Tan, J. B., Visan, I. and Guidos, C. J. (2003). Notch signalling in development and disease. *Clin Genet* 64, 461-72.

Harvey, K. and Tapon, N. (2007). The Salvador-Warts-Hippo pathway - an emerging tumour-suppressor network. *Nat Rev Cancer* 7, 182-91.

Hasson, P. and Paroush, Z. (2007). Crosstalk between the EGFR and other signalling pathways at the level of the global transcriptional corepressor Groucho/TLE. *Br J Cancer* 96 Suppl, R21-5.

Hernan, I., Roig, I., Martin, B., Gamundi, M. J., Martinez-Gimeno, M. and Carballo, M. (2004). De novo germline mutation in the serine-threonine kinase STK11/LKB1 gene associated with Peutz-Jeghers syndrome. *Clin Genet* 66, 58-62.

Hietakangas, V. and Cohen, S. M. (2009). Regulation of tissue growth through nutrient sensing. *Annu Rev Genet* 43, 389-410.

Hoeller, D., Volarevic, S. and Dikic, I. (2005). Compartmentalization of growth factor receptor signalling. *Curr Opin Cell Biol* 17, 107-11.

Hoffmans, R. and Basler, K. (2004). Identification and in vivo role of the Armadillo-Legless interaction. *Development* 131, 4393-400.

Hombria, J. C. and Sotillos, S. (2008). Disclosing JAK/STAT links to cell adhesion and cell polarity. *Semin Cell Dev Biol* 19, 370-8.

Horvitz, H. R. and Sternberg, P. W. (1991). Multiple intercellular signalling systems control the development of the Caenorhabditis elegans vulva. *Nature* 351, 535-541.

Hou, S. X., Zheng, Z., Chen, X. and Perrimon, N. (2002). The Jak/STAT pathway in model organisms: emerging roles in cell movement. *Dev Cell* 3, 765-78.

Huang, A. M. and Rubin, G. M. (2000). A Misexpression Screen Identifies Genes That Can Modulate RAS1 Pathway Signalling in Drosophila melanogaster. *Genetics* 156, 1219-1230.

Igaki, T. (2009). Correcting developmental errors by apoptosis: lessons from Drosophila JNK signalling. *Apoptosis* 14, 1021-8.

Inoki, K., Corradetti, M. N. and Guan, K. L. (2005). Dysregulation of the TSC-mTOR pathway in human disease. *Nat Genet* 37, 19-24.

Irish, V. F. and Gelbart, W. M. (1987). The decapentaplegic gene is required for dorsal-ventral patterning of the Drosophila embryo. *Genes Dev* 1, 868-79.

Jackson, S. M., Nakato, H., Sugiura, M., Jannuzi, A., Oakes, R., Kaluza, V., Golden, C. and Selleck, S. B. (1997). dally, a Drosophila glypican, controls cellular responses to the TGF-beta-related morphogen, Dpp. *Development* 124, 4113-4120.

Jacob, L. and Lum, L. (2007). Deconstructing the hedgehog pathway in development and disease. *Science* 318, 66-8.

Jacobs, C. I. (2008). A review of the role of insulin-like growth factor 2 in malignancy and its potential as a modifier of radiation sensitivity. *Clin Oncol (R Coll Radiol)* 20, 345-52.

Jang, A. C., Starz-Gaiano, M. and Montell, D. J. (2007). Modeling migration and metastasis in Drosophila. *J Mammary Gland Biol Neoplasia* 12, 103-14.

Janic, A., Mendizabal, L., Llamazares, S., Rossell, D. and Gonzalez, C. (2010). Ectopic expression of germline genes drives malignant brain tumor growth in Drosophila. *Science* 330, 1824-7.

Janknecht, R., Wells, N. J. and Hunter, T. (1998). TGF-beta-stimulated cooperation of smad proteins with the coactivators CBP/p300. *Genes Dev* 12, 2114-9.

Januschke, J. and Gonzalez, C. (2008). Drosophila asymmetric division, polarity and cancer. *Oncogene* 27, 6994-7002.

Jiang, Z., Li, X., Hu, J., Zhou, W., Jiang, Y., Li, G. and Lu, D. (2006). Promoter hypermethylation-mediated down-regulation of LATS1 and LATS2 in human astrocytoma. *Neurosci Res* 56, 450-8.

Jin, T. (2008). The WNT signalling pathway and diabetes mellitus. *Diabetologia* 51, 1771-80.

Jones, S. M. and Kazlauskas, A. (2001). Growth factor-dependent signalling and cell cycle progression. *Chem Rev* 101, 2413-23.

Kango-Singh, M. and Halder, G. (2004). Drosophila as an emerging model to study metastasis. *Genome Biol* 5, 216.

Kango-Singh, M. and Singh, A. (2009). Regulation of organ size: insights from the Drosophila Hippo signalling pathway. *Dev Dyn* 238, 1627-37.

Karim, F. D., Chang, H. C., Therrien, M., Wassarman, D. A., Laverty, T. and Rubin, G. M. (1996). A Screen for Genes That Function Downstream of Ras1 During Drosophila Eye Development. *Genetics* 143, 315-329.

Kataoka, H. (2009). EGFR ligands and their signalling scissors, ADAMs, as new molecular targets for anticancer treatments. *J Dermatol Sci* 56, 148-53.

Kim, N. C. and Marques, G. (2010). Identification of downstream targets of the bone morphogenetic protein pathway in the Drosophila nervous system. *Dev Dyn* 239, 2413-25.

Kim, E. K. and Choi, E. J. Pathological roles of MAPK signalling pathways in human diseases. *Biochim Biophys Acta* 1802, 396-405.

Kimelman, D. (2006). Mesoderm induction: from caps to chips. *Nat Rev Genet* 7, 360-72.

Kleino, A., Valanne, S., Ulvila, J., Kallio, J., Myllymaki, H., Enwald, H., Stoven, S., Poidevin, M., Ueda, R., Hultmark, D. et al. (2005). Inhibitor of apoptosis 2 and TAK1-binding protein are components of the Drosophila Imd pathway. *EMBO J* 24, 3423-34.

Kuan, C. T., Wikstrand, C. J. and Bigner, D. D. (2001). EGF mutant receptor vIII as a molecular target in cancer therapy. *Endocr Relat Cancer* 8, 83-96.

Kumar, J. P. (2001). Signalling pathways in Drosophila and vertebrate retinal development. *Nat Rev Genet* 2, 846-57.

Lage, P., Jan, Y. N. and Jarman, A. P. (1997). Requirement for EGF receptor signalling in neural recruitment during formation of Drosophila chordotonal sense organ clusters. *Curr Biol* 7, 166-75.

Le Bras, S., Loyer, N. and Le Borgne, R. (2011). The multiple facets of ubiquitination in the regulation of notch signalling pathway. *Traffic* 12, 149-61.

Lecuit, T. and Cohen, S. M. (1998). Dpp receptor levels contribute to shaping the Dpp morphogen gradient in the Drosophila wing imaginal disc. *Development* 125, 4901-7.

Lindquist, R., Ottina, K., Wheeler1, D., Hsu, P., Thoreen, C., Guertin, D., Ali, S., Sengupta, S., Shaul, Y., Lamprecht, M. et al. (2011). Genome-scale RNAi on living-cell microarrays identifies novel regulators of Drosophila melanogaster TORC1–S6K pathway signalling *Genome Res.* 21, 433-446.

Logan, C. Y. and Nusse, R. (2004). The Wnt signalling pathway in development and disease. *Annu Rev Cell Dev Biol* 20, 781-810.

Luo, K., Stroschein, S. L., Wang, W., Chen, D., Martens, E., Zhou, S. and Zhou, Q. (1999). The Ski oncoprotein interacts with the Smad proteins to repress TGFbeta signalling. *Genes Dev* 13, 2196-206.

Lum, L., Yao, S., Mozer, B., Rovescalli, A., Von Kessler, D., Nirenberg, M. and Beachy, P. A. (2003). Identification of Hedgehog pathway components by RNAi in Drosophila cultured cells. *Science* 299, 2039-45.

Lupo, G., Harris, W. A. and Lewis, K. E. (2006). Mechanisms of ventral patterning in the vertebrate nervous system. *Nat Rev Neurosci* 7, 103-14.

Ma, X. M. and Blenis, J. (2009). Molecular mechanisms of mTOR-mediated translational control. *Nat Rev Mol Cell Biol* 10, 307-18.

Mahoney, M. B., Parks, A. L., Ruddy, D. A., Tiong, S. Y. K., Esengil, H., Phan, A. C., Philandrinos, P., Winter, C. G., Chatterjee, R., Huppert, K. et al. (2006). Presenilin-Based Genetic Screens in Drosophila melanogaster Identify Novel Notch Pathway Modifiers. *Genetics* 172, 2309-2324.

Massague, J., Blain, S. W. and Lo, R. S. (2000). TGFbeta signalling in growth control, cancer, and heritable disorders. *Cell* 103, 295-309.

Massague, J. and Wotton, D. (2000). Transcriptional control by the TGF-beta/Smad signalling system. *EMBO J* 19, 1745-54.

Matallanas, D., Romano, D., Hamilton, G., Kolch, W. and O'Neill, E. (2008). A Hippo in the ointment: MST signalling beyond the fly. *Cell Cycle* 7, 879-84.

Matthews, K. A., Kaufman, T. C. and Gelbart, W. M. (2005). Research resources for Drosophila: the expanding universe. *Nat Rev Genet* 6, 179-93.

Mendelsohn, J. and Baselga, J. (2000). The EGF receptor family as targets for cancer therapy. *Oncogene* 19, 6550-65.

Meyers, A. J., Shah, R. R., Gottlieb, P. A. and Zipris, D. (2010). Altered Toll-like receptor signalling pathways in human type 1 diabetes. *J Mol Med* 88, 1221-31.

McNeill, H. and Woodgett, J. R. (2010). When pathways collide: collaboration and connivance among signalling proteins in development. *Nat Rev Mol Cell Biol* 11, 404-13.

Milan, M., Campuzano, S. and Garcia-Bellido, A. (1996). Cell cycling and patterned cell proliferation in the wing primordium of Drosop[hila. *P.N.A.S.* 93, 640-645.

Miller, J. P., Holcomb, J., Al-Ramahi, I., de Haro, M., Gafni, J., Zhang, N., Kim, E., Sanhueza, M., Torcassi, C., Kwak, S. et al. (2010). Matrix metalloproteinases are modifiers of huntingtin proteolysis and toxicity in Huntington's disease. *Neuron* 67, 199-212.

Mills, I. G. (2007). The interplay between clathrin-coated vesicles and cell signalling. *Semin Cell Dev Biol* 18, 459-70.

Miura, G. I., Buglino, J., Alvarado, D., Lemmon, M. A., Resh, M. D. and Treisman, J. E. (2006). Palmitoylation of the EGFR ligand Spitz by Rasp increases Spitz activity by restricting its diffusion. *Dev Cell* 10, 167-76.

Miyazono, K., Kamiya, Y. and Morikawa, M. (2010). Bone morphogenetic protein receptors and signal transduction. *J Biochem* 147, 35-51.

Miyazono, K., Maeda, S. and Imamura, T. (2005). BMP receptor signalling: transcriptional targets, regulation of signals, and signalling cross-talk. *Cytokine Growth Factor Rev* 16, 251-63.

Mok, G. F. and Sweetman, D. (2011). Many routes to the same destination: lessons from skeletal muscle development. *Reproduction* 141, 301-12.

Molnar, C., Lopez-Varea, A., Hernandez, R. and de Celis, J. F. (2006). A gain-of-function screen identifying genes required for vein formation in the Drosophila melanogaster wing. *Genetics* 174, 1635-59.

Moussian, B. and Roth, S. (2005). Dorsoventral axis formation in the Drosophila embryo--shaping and transducing a morphogen gradient. *Curr Biol* 15, R887-99.

Mukherjee, T., Schafer, U. and Zeidler, M. P. (2006). Identification of Drosophila Genes Modulating Janus Kinase/Signal Transducer and Activator of Transcription Signal Transduction. *Genetics* 172, 1683-1697.

Muller, D., Kugler, S. J., Preiss, A., Maier, D. and Nagel, A. C. (2005a). Genetic Modifier Screens on Hairless Gain-of-Function Phenotypes Reveal Genes Involved in Cell Differentiation, Cell Growth and Apoptosis in Drosophila melanogaster. *Genetics* 171, 1137-1152.

Muller, P., Kuttenkeuler, D., Gesellchen, V., Zeidler, M. P. and Boutros, M. (2005b). Identification of JAK/STAT signalling components by genome-wide RNA interference. *Nature* 436, 871-5.

Mummery-Widmer, J. L., Yamazaki, M., Stoeger, T., Novatchkova, M., Bhalerao, S., Chen, D., Dietzl, G., Dickson, B. J. and Knoblich, J. A. (2009). Genome-wide analysis of Notch signalling in Drosophila by transgenic RNAi. *Nature* 458, 987-92.

Neufeld, T., de la Cruz, A., Johnston, L. and Edgar, B. (1998). Coordination of growth and cell division in the Drosophila wing. *Cell* 93, 1183-1193.

Nusse, R. (1999). WNT targets. Repression and activation. *Trends Genet* 15, 1-3.

Nusslein-Volhard, C. and Wieschaus, E. (1980). Mutations affecting segment number and polarity in Drosophila. *Nature* 287, 795-801.

Nybakken, K., Vokes, S. A., Lin, T. Y., McMahon, A. P. and Perrimon, N. (2005). A genome-wide RNA interference screen in Drosophila melanogaster cells for new components of the Hh signalling pathway. *Nat Genet* 37, 1323-32.

O'Neill, L. A. (2003). Therapeutic targeting of Toll-like receptors for inflammatory and infectious diseases. *Curr Opin Pharmacol* 3, 396-403.

O'Sullivan, L. A., Liongue, C., Lewis, R. S., Stephenson, S. E. and Ward, A. C. (2007). Cytokine receptor signalling through the Jak-Stat-Socs pathway in disease. *Mol Immunol* 44, 2497-506.

Overholtzer, M., Zhang, J., Smolen, G. A., Muir, B., Li, W., Sgroi, D. C., Deng, C. X., Brugge, J. S. and Pan, D. (2010). The hippo signalling pathway in development and cancer. *Dev Cell* 19, 491-505.

Pajni-Underwood, S., Wilson, C. P., Elder, C., Mishina, Y. and Lewandoski, M. (2007). BMP signals control limb bud interdigital programmed cell death by regulating FGF signalling *Development* 134, 2359-2368.

Parks, A. L., Turner, F. R. and Muskavitch, M. A. T. (1995). Relationships between complex Delta expression and the specification of retinal cell fates during Drosophila eye development. *Mech. Dev.* 50, 201-216.

Peacock, C. D., Wang, Q., Gesell, G. S., Corcoran-Schwartz, I. M., Jones, E., Kim, J., Devereux, W. L., Peifer, M. and Pham, A. D., Muller, S. and Sauer, F. (1999). Mesoderm-determining transcription in Drosophila is alleviated by mutations in TAF(II)60 and TAF(II)110. *Mech Dev* 84, 3-16.

Perea, D., Terriente, J. and Diaz-Benjumea, F. J. (2009). Temporal and spatial windows delimit activation of the outer ring of wingless in the Drosophila wing. *Dev Biol* 328, 445-55.

Perrimon, N. and McMahon, A. P. (1999). Negative feedback mechanisms and their roles during pattern formation. *Cell* 97, 13-16.

Petcherski, A. G. and Kimble, J. (2000). Mastermind is a putative activator for Notch. *Curr Biol* 10, R471-3.

Pfeifer, A. C., Timmer, J. and Klingmuller, U. (2008). Systems biology of JAK/STAT signalling. *Essays Biochem* 45, 109-20.

Pfeiffer, S. and Vincent, J. P. (1999). Signalling at a distance: transport of Wingless in the embryonic epidermis of Drosophila. *Semin Cell Dev Biol* 10, 303-9.

Pi, H. and Chien, C. T. (2007). Getting the edge: neural precursor selection. *J Biomed Sci* 14, 467-73.

Piddini, E. and Vincent, J. P. (2003). Modulation of developmental signals by endocytosis: different means and many ends. *Curr Opin Cell Biol* 15, 474-81.

Polakis, P. (2000). Wnt signalling in oncogenesis and embryogenesis--a look outside the nucleus. *Science* 287, 1606-9.

Pouponnot, C., Jayaraman, L. and Massague, J. (1998). Physical and functional interaction of SMADs and p300/CBP. *J Biol Chem* 273, 22865-8.

Qi, C., Zhu, Y. T., Hu, L. and Zhu, Y. J. (2009). Identification of Fat4 as a candidate tumor suppressor gene in breast cancers. *Int J Cancer* 124, 793-8.

Raftery, L. A., Twombly, V., Wharton, K. and Gelbart, W. M. (1995). Genetic screens to identify elements of the decapentaplegic signalling pathway in Drosophila. *Genetics* 139, 241-54.

Raftery, L. A. and Sutherland, D. J. (1999). TGF-beta family signal transduction in Drosophila development: from Mad to Smads. *Dev Biol* 210, 251-68.

Rane, S. G. and Reddy, E. P. (2000). Janus kinases: components of multiple signalling pathways. *Oncogene* 19, 5662-79.

Read, R. D., Cavenee, W. K., Furnari, F. B. and Thomas, J. B. (2009). A drosophila model for EGFR-Ras and PI3K-dependent human glioma. *PLoS Genet* 5, e1000374.

Read, R. D., Goodfellow, P. J., Mardis, E. R., Novak, N., Armstrong, J. R. and Cagan, R. L. (2005a). A Drosophila Model of Multiple Endocrine Neoplasia Type 2. *Genetics* 171, 1057-1081.

Rebay, I., Chen, F., Hsiao, F., Kolodziej, P. A., Kuang, B. H., Laverty, T., Suh, C., Voas, M., Williams, A. and Rubin, G. M. (2000). A Genetic Screen for Novel Components of the Ras/Mitogen-Activated Protein Kinase Signalling Pathway That Interact With the yan Gene of Drosophila Identifies split ends, a New RNA Recognition Motif-Containing Protein. *Genetics* 154, 695-712.

Reiter, L. T., Potocki, L., Chien, S., Gribskov, M. and Bier, E. (2001). A systematic analysis of human disease-associated gene sequences in Drosophila melanogaster. *Genome Res* 11, 1114-25.

Resnick, L. and Fennell, M. (2004). Targeting JNK3 for the treatment of neurodegenerative disorders. *Drug Discov Today* 9, 932-9.

Resnik-Docampo, M. and de Celis, J. F. (2011). MAP4K3 is a component of the TORC1 signalling complex that modulates cell growth and viability in Drosophila melanogaster. *PLoS One* 6, e14528.

Rhodes, J. T., Huff, C. A., Beachy, P. A. et al. (2007). Hedgehog signalling maintains a tumor stem cell compartment in multiple myeloma. *Proc Natl Acad Sci U S A* 104, 4048-53.

Ricci, R., Sumara, G., Sumara, I., Rozenberg, I., Kurrer, M., Akhmedov, A., Hersberger, M., Eriksson, U., Eberli, F. R., Becher, B. et al. (2004). Requirement of JNK2 for scavenger receptor A-mediated foam cell formation in atherogenesis. *Science* 306, 1558-61.

Rooke, H. M. and Crosier, K. E. (2001). The smad proteins and TGFbeta signalling: uncovering a pathway critical in cancer. *Pathology* 33, 73-84.

Roose, J., Molenaar, M., Peterson, J., Hurenkamp, J., Brantjes, H., Moerer, P., van de Wetering, M., Destree, O. and Clevers, H. (1998). The Xenopus Wnt effector XTcf-3 interacts with Groucho-related transcriptional repressors. *Nature* 395, 608-12.

Rorth, P., Szabo, K., Bailey, A., Laverty, T., Rehm, J., Rubin, G. M., Weigmann, K., Milan, M., Benes, V., Ansorge, W. et al. (1998). Systematic gain-of-function genetics in Drosophila. *Development* 125, 1049-57.

Rosner, M., Hanneder, M., Siegel, N., Valli, A., Fuchs, C. and Hengstschlager, M. (2008). The mTOR pathway and its role in human genetic diseases. *Mutat Res* 659, 284-92.

Ruiz-Gomez, A., Molnar, C., Holguin, H., Mayor, F., Jr. and de Celis, J. F. (2007). The cell biology of Smo signalling and its relationships with GPCRs. *Biochim Biophys Acta* 1768, 901-12.

Ruiz i Altaba, A., Sanchez, P. and Dahmane, N. (2002). Gli and hedgehog in cancer: tumours, embryos and stem cells. *Nat Rev Cancer* 2, 361-72.

Sang, T. K. and Jackson, G. R. (2005). Drosophila models of neurodegenerative disease. *NeuroRx* 2, 438-46.

Sato, M., Kojima, T., Michiue, T. and Saigo, K. (1999). Bar homeobox genes are latitudinal prepattern genes in the developing Drosophila notum whose expression is regulated by the concerted functions of decapentaplegic and wingless. *Development* 126, 1457-1466.

Schindler, C. W. (2002). Series introduction. JAK-STAT signalling in human disease. *J Clin Invest* 109, 1133-7.

Schwanbeck, R., Martini, S., Bernoth, K. and Just, U. (2010). The Notch signalling pathway: Molecular basis of cell context dependency. *Eur J Cell Biol*.

Schubbert, S., Shannon, K. and Bollag, G. (2007). Hyperactive Ras in developmental disorders and cancer. *Nat Rev Cancer* 7, 295-308.

Seidel, C., Schagdarsurengin, U., Blumke, K., Wurl, P., Pfeifer, G. P., Hauptmann, S., Taubert, H. and Dammann, R. (2007). Frequent hypermethylation of MST1 and MST2 in soft tissue sarcoma. *Mol Carcinog* 46, 865-71.

Seto, E. S. and Bellen, H. J. (2004). The ins and outs of Wingless signalling. *Trends Cell Biol* 14, 45-53.

Shilo, B. Z. (2003). Signalling by the Drosophila epidermal growth factor receptor pathway during development. *Exp Cell Res* 284, 140-9.

Smith, W. W., Gorospe, M. and Kusiak, J. W. (2006). Signalling mechanisms underlying Abeta toxicity: potential therapeutic targets for Alzheimer's disease. *CNS Neurol Disord Drug Targets* 5, 355-61.

So, E. Y. and Ouchi, T. (2010). The application of Toll like receptors for cancer therapy. *Int J Biol Sci* 6, 675-81.

Sorkin, A. and von Zastrow, M. (2009). Endocytosis and signalling: intertwining molecular networks. *Nat Rev Mol Cell Biol* 10, 609-22.

Sotillos, S. and De Celis, J. F. (2005). Interactions between the Notch, EGFR, and decapentaplegic signalling pathways regulate vein differentiation during Drosophila pupal wing development. *Dev Dyn* 232, 738-52.

Stanisic, V., Lonard, D. M. and O'Malley, B. W. (2010). Modulation of steroid hormone receptor activity. *Prog Brain Res* 181, 153-76.

Steinhardt, A. A., Gayyed, M. F., Klein, A. P., Dong, J., Maitra, A., Pan, D., Montgomery, E. A. and Anders, R. A. (2008). Expression of Yes-associated protein in common solid tumors. *Hum Pathol* 39, 1582-9.

Steinhauer, J. and Treisman, J. E. (2009). Lipid-modified morphogens: functions of fats. *Curr Opin Genet Dev* 19, 308-14.

Stern, C. (1954). Two or three bristles. *Am. Scientist*, 213-247.

Steventon, B., Araya, C., Linker, C., Kuriyama, S. and Mayor, R. (2009). Differential requirements of BMP and Wnt signalling during gastrulation and neurulation define two steps in neural crest induction. *Development* 136, 771-9.

Stroschein, S. L., Wang, W., Zhou, S., Zhou, Q. and Luo, K. (1999). Negative feedback regulation of TGF-beta signalling by the SnoN oncoprotein. *Science* 286, 771-4.

Su, G. H., Hilgers, W., Shekher, M. C., Tang, D. J., Yeo, C. J., Hruban, R. H. and Kern, S. E. (1998). Alterations in pancreatic, biliary, and breast carcinomas support MKK4 as a genetically targeted tumor suppressor gene. *Cancer Res* 58, 2339-42.

Su, M. A., Wisotzkey, R. G. and Newfeld, S. J. (2001). A Screen for Modifiers of decapentaplegic Mutant Phenotypes Identifies lilliputian, the Only Member of the Fragile-X/Burkitt's Lymphoma Family of Transcription Factors in Drosophila melanogaster. *Genetics* 157, 717-725.

Sumara, G., Belwal, M. and Ricci, R. (2005). "Jnking" atherosclerosis. *Cell Mol Life Sci* 62, 2487-94.

Sun, Y., Liu, X., Eaton, E. N., Lane, W. S., Lodish, H. F. and Weinberg, R. A. (1999a). Interaction of the Ski oncoprotein with Smad3 regulates TGF-beta signalling. *Mol Cell* 4, 499-509.

Sun, Y., Liu, X., Ng-Eaton, E., Lodish, H. F. and Weinberg, R. A. (1999b). SnoN and Ski protooncoproteins are rapidly degraded in response to transforming growth factor beta signalling. *Proc Natl Acad Sci U S A* 96, 12442-7.

Tabata, T. and Kornberg, T. B. (1994). Hedgehog is a signalling protein with a key role in patterning Drosophila imaginal discs. *Cell* 76, 89-102.

Taguchi, A., Sawamoto, K. and Okano, H. (2000). Mutations Modulating the Argos-Regulated Signalling Pathway in Drosophila Eye Development. *Genetics* 154, 1639-1648.

Taipale, J. and Beachy, P. A. (2001). The Hedgehog and Wnt signalling pathways in cancer. *Nature* 411, 349-54.

Tartaglia, M. and Gelb, B. D. (2005). Noonan syndrome and related disorders: genetics and pathogenesis. *Annu Rev Genomics Hum Genet* 6, 45-68.

Tazi-Ahnini, R., Cork, M. J., Wengraf, D., Wilson, A. G., Gawkrodger, D. J., Birch, M. P., Messenger, A. G. and McDonagh, A. J. (2003). Notch4, a non-HLA gene in the MHC is strongly associated with the most severe form of alopecia areata. *Hum Genet* 112, 400-3.

ten Dijke, P. and Arthur, H. M. (2007). Extracellular control of TGFbeta signalling in vascular development and disease. *Nat Rev Mol Cell Biol* 8, 857-69.

Thompson, B. J. (2010). Developmental control of cell growth and division in Drosophila. *Curr Opin Cell Biol* 22, 788-94.

Tomoyasu, Y., Nakamura, M. and Ueno, N. (1998). Role of Dpp signalling in prepattern formation of the dorsocentral mechanosensory organ in Drosophila melanogaster. *Development* 125, 4215-4224.

Towers, M. and Tickle, C. (2009). Generation of pattern and form in the developing limb. *Int J Dev Biol* 53, 805-12.

Turenchalk, G. S., St John, M. A., Tao, W. and Xu, T. (1999). The role of lats in cell cycle regulation and tumorigenesis. *Biochim Biophys Acta* 1424, M9-M16.

Tyler, D. M., Li, W., Zhuo, N., Pellock, B. and Baker, N. E. (2007). Genes affecting cell competition in Drosophila. *Genetics* 175, 643-57.

Urban, S., Lee, J. R. and Freeman, M. (2002). A family of Rhomboid intramembrane proteases activates all Drosophila membrane-tethered EGF ligands. *EMBO J* 21, 4277-86.

Ujike, H., Takehisa, Y., Takaki, M., Tanaka, Y., Nakata, K., Takeda, T., Kodama, M., Fujiwara, Y., Yamamoto, A. and Kuroda, S. (2001). NOTCH4 gene polymorphism and susceptibility to schizophrenia and schizoaffective disorder. *Neurosci Lett* 301, 41-4.

Valanne, S., Wang, J. H. and Ramet, M. (2011). The Drosophila Toll signalling pathway. *J Immunol* 186, 649-56.

van Der Heide, L. P., Hoekman, M. F. and Smidt, M. P. (2004). The ins and outs of FoxO shuttling: mechanisms of FoxO translocation and transcriptional regulation. *Biochem J* 380, 297-309.

van Slegtenhorst, M., de Hoogt, R., Hermans, C., Nellist, M., Janssen, B., Verhoef, S., Lindhout, D., van den Ouweland, A., Halley, D., Young, J. et al. (1997). Identification of the tuberous sclerosis gene TSC1 on chromosome 9q34. *Science* 277, 805-8.

Vargesson, N., Patel, K., Lewis, J. and Tickle, C. (1998). Expression patterns of Notch1, Serrate1, Serrate2 and Delta1 in tissues of the developing chick limb. *Mech Dev* 77, 197-9.

Verheyen, E. M., Purcell, K. J., Fortini, M. E. and Artavanis-Tsakonas, S. (1996). Analysis of Dominant Enhancers and Suppressors of Activated Notch in Drosophila. *Genetics* 144, 1127-1141.

Vidal, M. and Cagan, R. L. (2006). Drosophila models for cancer research. *Curr Opin Genet Dev* 16, 10-6.

Vivekanand, P., Tootle, T. L. and Rebay, I. (2004). MAE, a dual regulator of the EGFR signalling pathway, is a target of the Ets transcription factors PNT and YAN. *Mech Dev* 121, 1469-79.

Vu Manh, T. P., Mokrane, M., Georgenthum, E., Flavigny, J., Carrier, L., Semeriva, M., Piovant, M. and Roder, L. (2005). Expression of cardiac myosin-binding protein-C (cMyBP-C) in Drosophila as a model for the study of human cardiomyopathies. *Hum Mol Genet* 14, 7-17.

Wackerhage, H. and Ratkevicius, A. (2008). Signal transduction pathways that regulate muscle growth. *Essays Biochem* 44, 99-108.

Waeber, G., Delplanque, J., Bonny, C., Mooser, V., Steinmann, M., Widmann, C., Maillard, A., Miklossy, J., Dina, C., Hani, E. H. et al. (2000). The gene MAPK8IP1, encoding islet-brain-1, is a candidate for type 2 diabetes. *Nat Genet* 24, 291-5.

Waite, K. A. and Eng, C. (2003). From developmental disorder to heritable cancer: it's all in the BMP/TGF-beta family. *Nat Rev Genet* 4, 763-73.

Waltzer, L. and Bienz, M. (1998). Drosophila CBP represses the transcription factor TCF to antagonize Wingless signalling. *Nature* 395, 521-5.

Waltzer, L. and Bienz, M. (1999). A function of CBP as a transcriptional co-activator during Dpp signalling. *EMBO J* 18, 1630-41.

Wechsler-Reya, R. and Scott, M. P. (2001). The developmental biology of brain tumors. *Annu Rev Neurosci* 24, 385-428.

Wei, J. and Hemmings, G. P. (2000). The NOTCH4 locus is associated with susceptibility to schizophrenia. *Nat Genet* 25, 376-7.

Wesley, C. S. (1999). Notch and wingless regulate expression of cuticle patterning genes. *Mol Cell Biol* 19, 5743-58.

Whitworth, A. J. and Russell, S. (2003). Temporally dynamic response to Wingless directs the sequential elaboration of the proximodistal axis of the Drosophila wing. *Dev Biol* 254, 277-88.

Wright, V. M., Vogt, K. L., Smythe, E. and Zeidler, M. P. (2011). Differential activities of the Drosophila JAK/STAT pathway ligands Upd, Upd2 and Upd3. *Cell Signal* 23, 920-7.

Wu, J. and Cohen, S. M. (2002). Repression of Teashirt marks the initiation of wing development. *Development* 129, 2411-8.

Wu, M., Pastor-Pareja, J. C. and Xu, T. (2010). Interaction between Ras(V12) and scribbled clones induces tumour growth and invasion. *Nature* 463, 545-8.

Yang, M., Nelson, D., Funakoshi, Y. and Padgett, R. W. (2004). Genome-wide microarray analysis of TGFbeta signalling in the Drosophila brain. *BMC Dev Biol* 4, 14.

Zavadil, J. and Böttinger, E. P. (2005). TGF-beta and epithelial-to-mesenchymal transitions. *Oncogene* 24, 5764-5774.

Zecca, M. and Struhl, G. (2002). Subdivision of the Drosophila wing imaginal disc by EGFR-mediated signaling. *Development* 129, 1357-1368.

Zender, L., Spector, M. S., Xue, W., Flemming, P., Cordon-Cardo, C., Silke, J., Fan, S. T., Luk, J. M., Wigler, M., Hannon, G. J. et al. (2006). Identification and validation of

oncogenes in liver cancer using an integrative oncogenomic approach. *Cell* 125, 1253-67.

Zeng, Q. and Hong, W. (2008). The emerging role of the hippo pathway in cell contact inhibition, organ size control, and cancer development in mammals. *Cancer Cell* 13, 188-92.

Zhou, S., Fujimuro, M., Hsieh, J. J., Chen, L., Miyamoto, A., Weinmaster, G. and Hayward, S. D. (2000). SKIP, a CBF1-associated protein, interacts with the ankyrin repeat domain of NotchIC To facilitate NotchIC function. *Mol Cell Biol* 20, 2400-10.

Zhu, H. and Lo, H. W. The Human Glioma-Associated Oncogene Homolog 1 (GLI1) Family of Transcription Factors in Gene Regulation and Diseases. *Curr Genomics* 11, 238-45.

Zhu, H. J. and Burgess, A. W. (2001). Regulation of transforming growth factor-beta signalling. *Mol Cell Biol Res Commun* 4, 321-30.

Zhu, J. and Mohan, C. (2010). Toll-like receptor signalling pathways--therapeutic opportunities. *Mediators Inflamm* 2010, 781235.

Zirin, J. D. and Mann, R. S. (2007). Nubbin and Teashirt mark barriers to clonal growth along the proximal-distal axis of the Drosophila wing. *Dev Biol* 304, 745-58.

Zoncu, R., Efeyan, A. and Sabatini, D. M. (2011). mTOR: from growth signal integration to cancer, diabetes and ageing. *Nat Rev Mol Cell Biol* 12, 21-35.
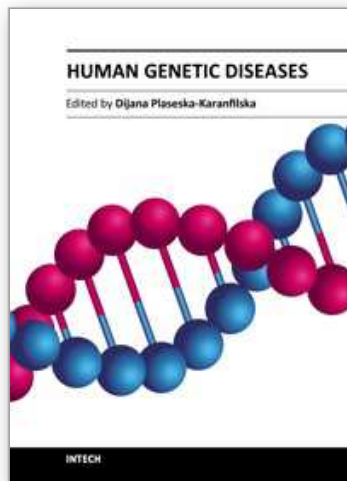
Human Genetic Diseases

Edited by Dr. Dijana Plaseska-Karanfilska

The genetics science is less than 150 years old, but its accomplishments have been astonishing. Genetics has become an indispensable component of almost all research in modern biology and medicine. Human genetic variation is associated with many, if not all, human diseases and disabilities. Nowadays, studies investigating any biological process, from the molecular level to the population level, use the â€œgenetic approachâ€ to gain understanding of that process. This book contains many diverse chapters, dealing with human genetic diseases, methods to diagnose them, novel approaches to treat them and molecular approaches and concepts to understand them. Although this book does not give a comprehensive overview of human genetic diseases, I believe that the sixteen book chapters will be a valuable resource for researchers and students in different life and medical sciences.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

INTECH
open science | open minds