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

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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).

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

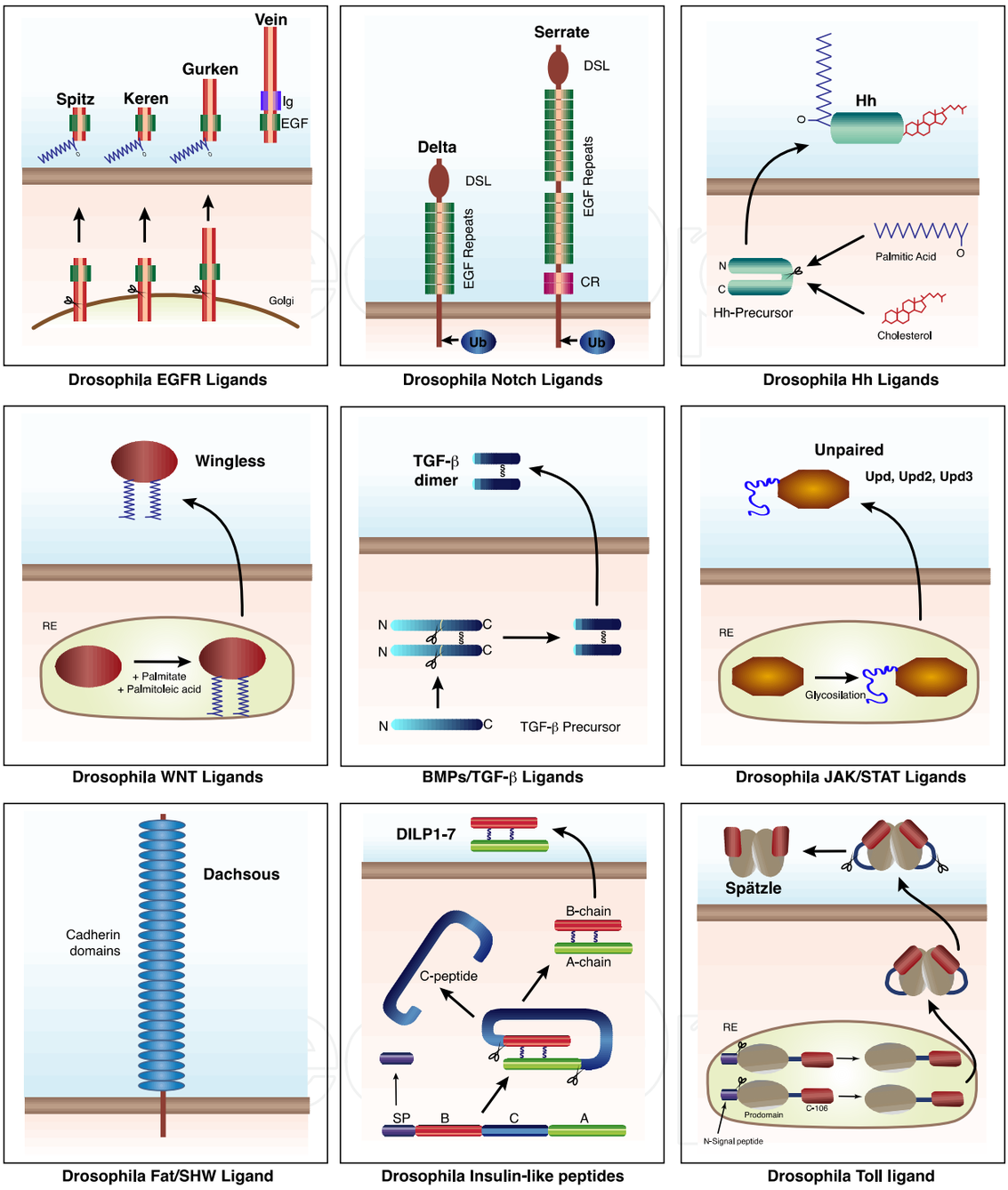

Fig. 1. Schematic representation of the ligands and their post-transcriptional modifications. Upper panels: EGFR, Notch and Hh ligands, middle panels: Wnt, BMP/TGFβ and JAK/STAT ligands and bottom panels (SWH, Insulin and Toll ligands.

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

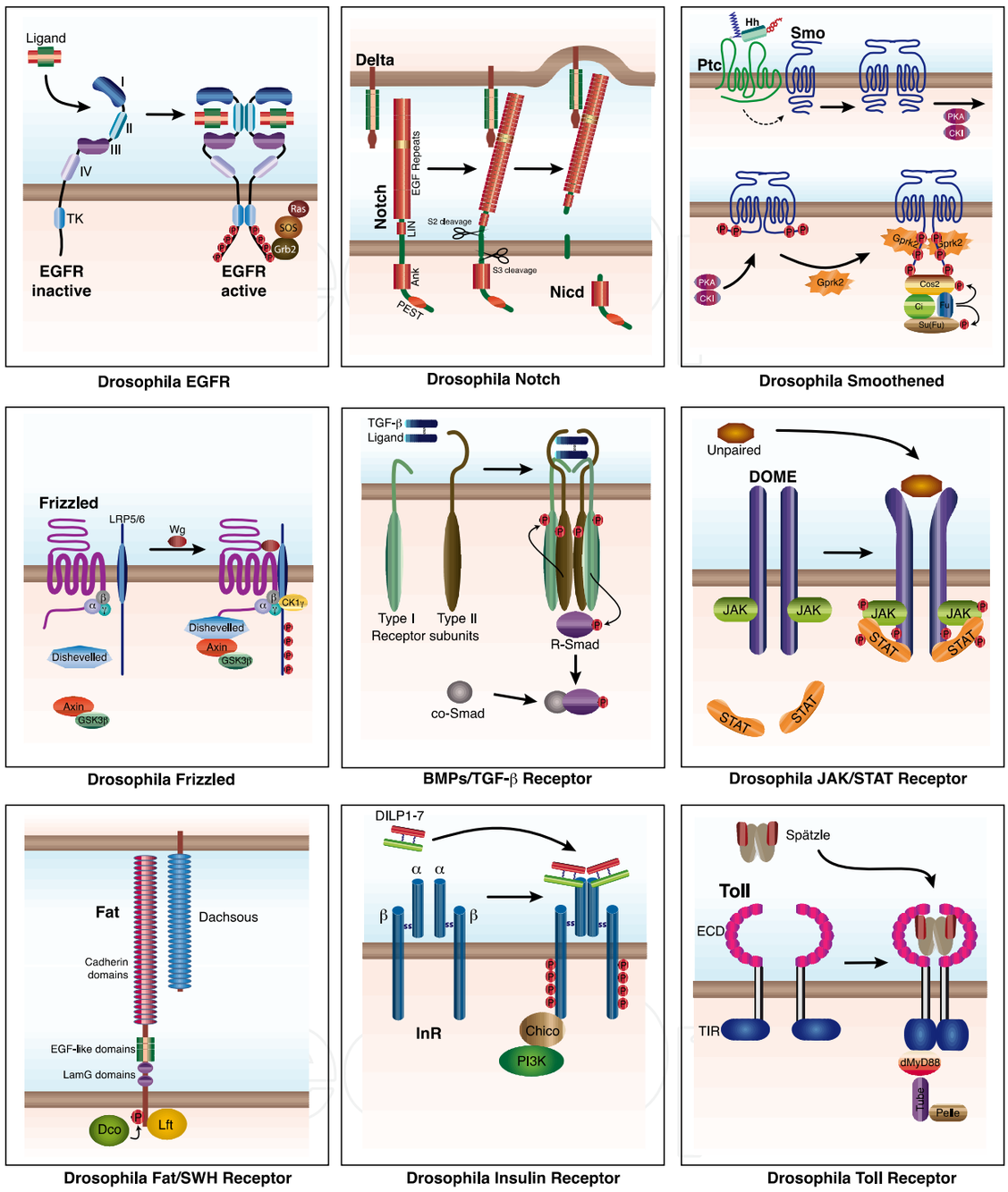

Fig. 2. Schematic representation of the receptors and their mechanisms of activation

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).

	TF		Activation of TF		Localization/State of TF		Co-TF	
Pathway / Organism	**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).

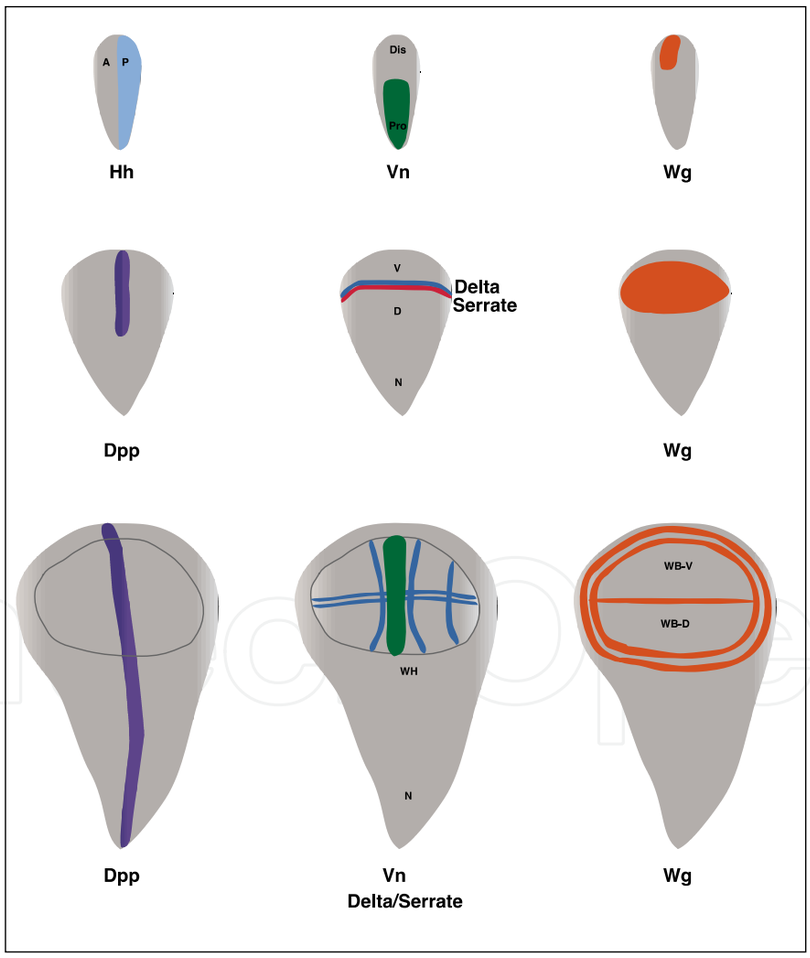

Fig. 3. Schematic representation of the wing disc during the second (upper panels), mid-third (middle panel) and late-third (bottom panel) larval instard, showing the expression of ligands in coloured stripes.

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

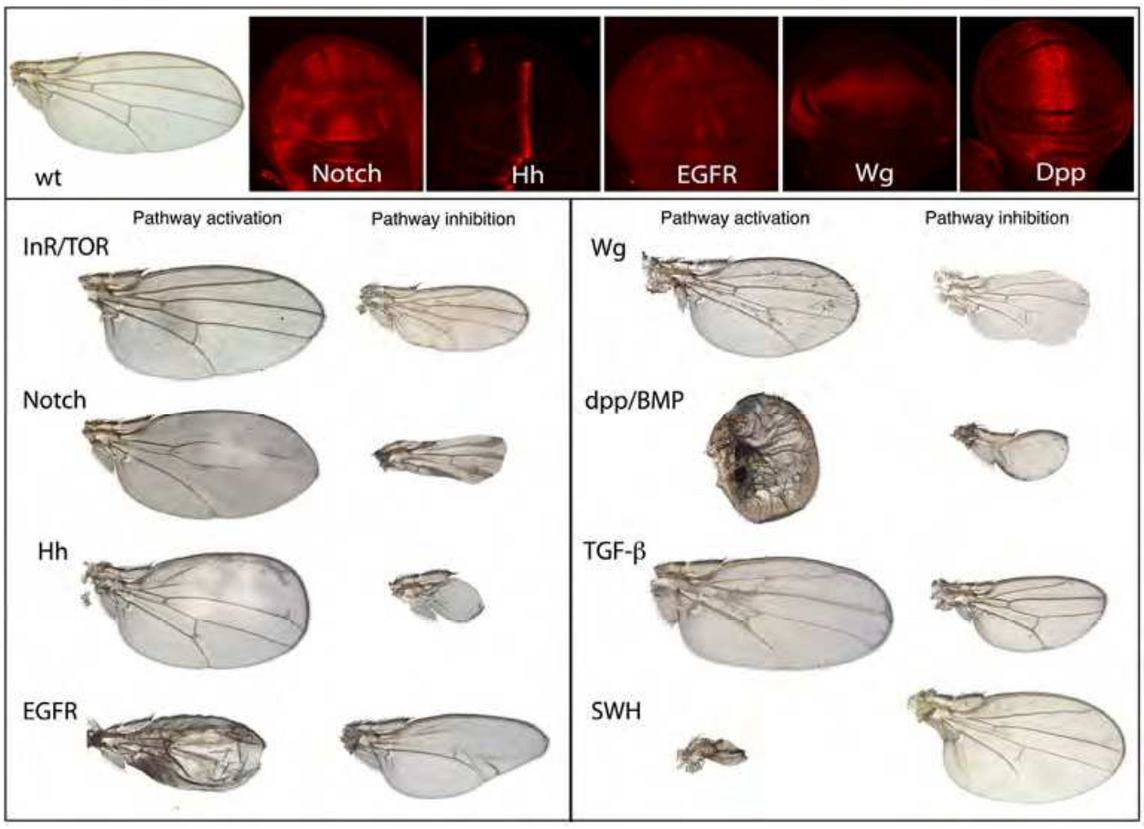

Fig. 4. Upper panel: Pictures of a wild type wing (wt, left) and third instar imaginal discs showing the domains of Notch, Hh, EGFR, Wg and Dpp signalling. Bottom panel: Pictures of mutant wings in which the activity of the InR/Tor, Notch, Hh and EGFR (left two columns), and Wg, dpp/BMP, TGF-β and SWH (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.

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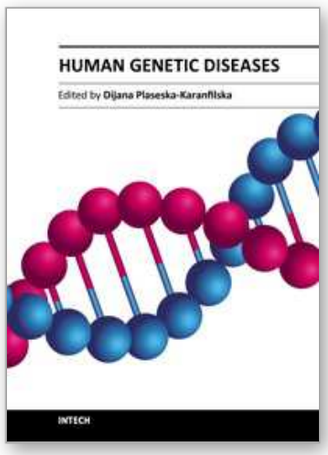

Human Genetic Diseases

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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.

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