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Cancer Stem Cells as a New Opportunity for Therapeutic Intervention

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1. Introduction

For several years, a new theory about the formation of tumors is gathering strength. This new theory sustains that, tumors, as most of adult tissues, contain a very small population of altered stem cells. These long lived tumor stem cell population through its capacity of cell renewal and differentiation would be the origin of the larger short lived population of malignant differentiated cells in the tumor. However, central questions are still pending to be solved such as; if tumors start with mutations in adult stem cells or if a more differentiated cell could acquire stem cell properties and develop and maintain the tumor bulk.

These tumor stem cells just like adult stem cells would also operate through specific signaling pathways, different to those in any other differentiated healthy cell of the adult or the tumor mass.

According to this theory, it is believed that relapses in patients treated with traditional therapeutic strategies like chemotherapy and even new anti-target agents are due to the fact that this type of treatment although having the capacity to destroy most of the tumor cells, would not affect the cancer stem cells. These residual tumor stem cells would therefore be the ones that in a shorter or longer time span would end up regenerating the tumor.

Thereby, new anti-target agents designed to block the signaling pathways that rule the activity of stem cells may be considered a new promising therapeutic strategy to avoid relapses to conventional treatments.

At the moment, large pharmaceutical companies are developing drugs that can block three signaling pathways considered critical for the maintenance of stem cells, the Notch pathway, the Wnt pathway and the Hedgehog pathway. These drugs have already shown promising efficacy and safety in clinical trials in different settings and tumor types. In this chapter we will review this issue with depth.

2. Stem cells and cancer stem cell theory

Stem Cells

In order to understand cancer stem cells a brief description of normal adult stem cells and the environment in which they live should be an indispensible requisite in this chapter.

Normal adult stem cells (SCs) are cells with the ability to continually repopulate the tissues that comprise the organ system in which they exist. One of their main properties is their differentiation capability which allows them to produce tissue-specific specialized daughter cells under certain conditions (Schöler, 2007). They also possess a self-renewal capability comprised by an asymmetric cell division in which one of the daughter cells is always a stem cell (self-renewal) while the other will be a transient amplifying precursor with high proliferative capacity which will undergo several symmetric divisions resulting in the generation of lineage-committed progenitors that will finally differentiate into non-cycling, terminally differentiated, mature cells (Bapat, 2007). Lastly, SCs have a high proliferative capacity even though they usually appear in a quiescent or slowly cycling state (Lobo et al. 2007).

SCs reside within a tissue microenvironment often described as *niche;* a stroma made up of differentiated cells which secrete a rich extracellular matrix and other factors essential for the tight regulation of the maintenance and renewal processes in organs or tissues (Fuchs et al. 2004). The niche microenvironment promotes adhesion and maintenance of the quiescent state of SC by inhibiting both proliferation and differentiation and, when needed, also regulates SC self-renewal, proliferation of the transit amplifying cell population and cell differentiation (Rizvi et al. 2005; Fuchs et al. 2004).

Cancer Stem Cell Theory

The idea of cancer being a pathology related with less mature cells was already introduced in 1858 by Rudolf Virchow. He laid the foundations for cell pathology suggesting that all cells arise from other cells ("*omnis cellula e cellula*"), and provided scientific basis for cancer through its microscopical and clinical observations which lead to the idea that cancer arises form an immature cell (Lobo et al. 2007).

Later on, in 1889, Sir S. Paget introduced the *soil and seed* hypothesis of metastasis suggesting that the distribution of metastases could not be due to chance alone and that only some tissues provide more optimal conditions for the growth of certain tumors (Paget, 1889). In his hypothesis, the *seed* would refer to the ostensible less mature tumor-initiating cell or stem cell from the primary tumor which would be the tumorigenic force behind tumor initiation, growth, metastasis and the cause of treatment resistance and relapse (reviewed in Pardal et al, 2003); while the *soil* would refer to the secondary site where the tumor would arise.

A variation of this idea was provided by the *homing* hypothesis which suggested that different organs could be able to attract different types of metastatic cells originated at the primary site through chemotactic mechanisms provided by signals secreted by cells at the future metastatic sites (Stetler-Stevenson 2001, Müller 2001, Strieter, 2001). In this hypothesis, the *seed* would produce cell surface receptors capable of recognizing secreted signals from the new site defined as the *soil*.

Although the mechanisms of tissue specificity of metastases still remains obscure, researchers have focused on small messenger molecules that may act as attractants and larger cell surface receptors which could guide the tumor-initiating cells or *seeds.* Müller (Müller et al, 2001) and Murphy (Murphy, 2001) focused on chemokines and their receptors as potential viable candidates for this *soil and seed* signaling. Murphy specifically proposes a "spatial and temporal code" made up of specific combinations of chemokines, chemokine receptors and adhesion molecules as being responsible for the neovascularization, metastasis, and immunosurveillance avoidance in tumors.

Cancer Stem Cells

Cancer Stem Cells (CSCs) are tumor cells different from the rest of the tumor bulk in that they can drive the growth and spread of a tumor (Lobo et al. 2007). They share their main characteristics with normal SCs and that is why they share a similar nomenclature. CSCs show self-renewal, certain potency as the can produce all the cell types that appear in a tumor through division and differentiation processes and have a high proliferative capacity although they usually appear in a quiescent state (Bhattacharyya et al. 2010; Lobo et al. 2007) which allows them to be more resistant to traditional anti-cancer drugs.

The main difference with SCs would be that the above processes in CSCs would be uncontrolled due to alterations in genes that encode for key signaling proteins or in the niche control and they therefore may give rise to aberrant tumorigenic tissues (Ishiguro et al. 2006; Weber et al. 2006; Clarke, 2005).

Disruption of the niche signal may also lead to either loss of SCs or malignant transformation of these SCs resulting in cancer (Bhattacharyya et al. 2010).

Several authors demonstrate that changes in the stability of the stroma lead to the induction of colorectal adenomas and invasive breast carcinomas amongst others (Ishiguro et al. 2006; Weber et al. 2006). Disruptive processes occurring in the niche during infection, inflammation, tissue damage, or chemical assault, could therefore be partly responsible of the changes that give rise to cancer stem cells (CSCs).

The discovery of tumor heterogeneity, where different cells within the tumor show different phenotypes gave rise to a CSC theory leaving behind the classical or stochastic model which stated that all neoplastic cells within a tumor have the same tumorigenic capacity but their ability to enter the cell cycle and find a permissive environment for growth would be a stochastic event that would occur with low probability (Dick, 2003; Lobo et al. 2007; Huntly & Gilliland,2005).

The CSC theory therefore suggests that a malignant tumor would be composed of a heterogeneous population of cells with different degrees of tumorigenic potential in which only a subset of cancer cells would be able to initiate and propagate the tumor. This theory arose from the fact that therapeutic approaches that aim the bulk of the tumor are not successful in avoiding relapses which must mean that not all cells in a tumor are the same. A subset of cells with different characteristics must achieve an extensive proliferation inducing the re-growth of the tumor (Reya et al. 2001). This phenomenon was proved by showing both in solid and hematological tumors that only a proportion of the tumor cells were clonogenic in culture and *in vivo* (Park et al. 1971; Fidler IJ et al. 1977).

The origin of these CSC is slightly controversial; its name suggests a SC origin although mutations in more differentiated progenitors could also give rise to CSCs (Figure 1).

The first hypothesis suggests that CSCs arise from stem cells with transforming mutations or epigenetic alterations that acquire a malignant phenotype. In a murine model of prostate cancer, a targeted suppression of the *PTEN* gene in luminal stem cells resulted in rapid formation of neoplasias and invasive carcinomas indicating a possible CSC origin in prostate cancers (Wang et al. 2009).

On the other hand, CSCs could be originated in a more committed cell progeny through maturation arrest of progenitor cells and the ability of these more differentiated cells to re-enter the cell cycle and undergo uncontrolled proliferation both mediated by mutational events that reactivate the self-renewal machinery (Bapat, 2007; Wang 2010).

In order to favor the appearance of CSCs several changes should occur such as: changes in the niche microenvironment, epigenetic deregulation and mutations in specific genes responsible for alterations in the cell cycle pattern, self-renewal, metabolism and differentiation processes and finally, amplification of these genetically altered populations (Bapat, 2007).

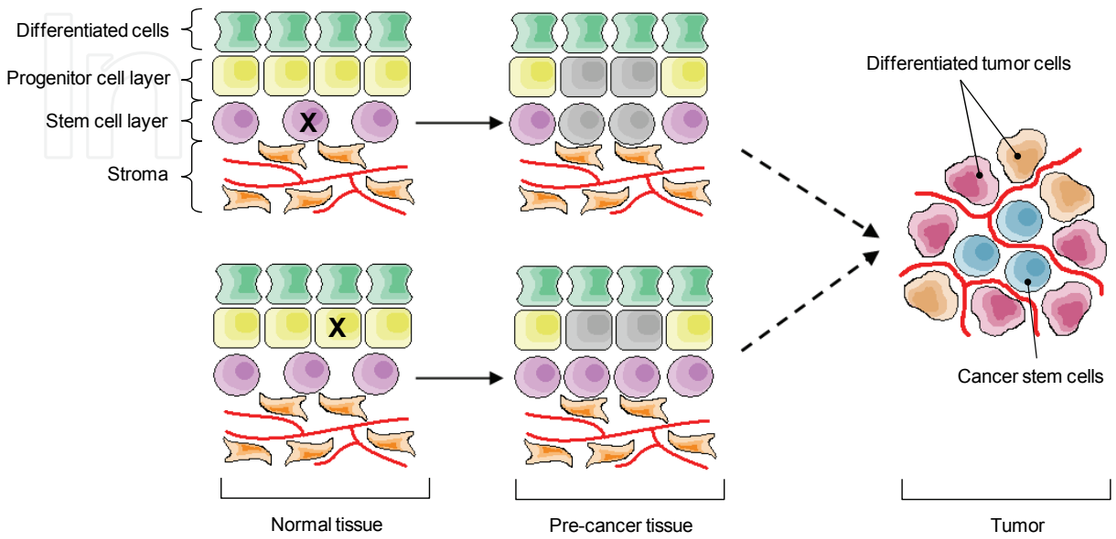

Fig. 1. Origin of CSCs.
CSCs may arise from the normal SC population due to spontaneous genetic or epigenetic changes or changes induced by disruption of the SC niche/stroma (**X**). The acquisition of malignant traits by SCs will be inherited by their progeny (grey cells). On the other hand, CSC origins could start in a more committed cell progeny through acquisition of self-renewal properties once again mediated by mutational events and giving rise to modified daughter cells (grey cells). Additional modifications of this partially modified progeny and subsequent cell divisions would then lead to the formation of CSCs and a heterogeneous tumor bulk.

3. Cancer stem cell pathways and new opportunities for therapeutic interventions

By definition, CSCs would maintain the self-renewal and differentiation capacities of SCs; thus it is likely that similarities exist in the pathways governing these processes in both normal and CSCs. Understanding the subjacent responsible molecular pathways that regulate these events in normal SCs is therefore extremely important for the design of drugs aimed to destroy CSCs and even avoid tumor relapse.
It has been suggested that specific signaling pathways such as Notch, Sonic Hedgehog (Shh) and Wingless (Wnt)-β-catenin are critical for self-renewal and differentiation in normal stem cells. In agreement with the CSC hypothesis, alterations in those genes that encode for signaling molecules belonging to these pathways have been found in human tumor samples suggesting that they are likely involved in tumor development and maintenance (Lobo et al, 2007; Sánchez-García et al. 2007). .

Hedgehog signaling pathway

The Hedgehog (Hh) signaling pathway plays a crucial role in human embryogenesis, but is largely inactive in adult tissues under normal conditions (Rubin and de Sauvage, 2006) The SHH signaling pathway is involved in the maintenance of normal adult stem cell population and expansion of progenitors (Ingham and McMahon, 2001).

The Hh gene family encodes several secreted glycoproteins such as Indian Hedgehog (IHH), Desert Hedgehog (DHH), and Sonic Hedgehog (SHH) (reviewed in Taipale & Beachy, 2001; Liu et al., 2005). The Hh pathway is unique in that the above ligands serve to relieve a series of repressive interactions between membrane receptors. In the absence of ligands, the transmembrane receptor Patched 1 (PTCH) blocks the smoothened (SMO) receptor, blocking its activity. The binding of the ligand to PTCH derepresses SMO, allowing the activation of the serine/threonine kinase Fused (Fu) which leads to the release of the transcription factor Gli from the sequestration by Suppressor of Fused (SuFu). Subsequently Gli proteins are able to translocate to the nucleus and regulate transcription of target genes involved in proliferation and differentiation such as cyclin D and c-myc (reviewed in Nybakken & Perrimon, 2002; Pasca di Magliano & Hebrok, 2003) (Figure 2).

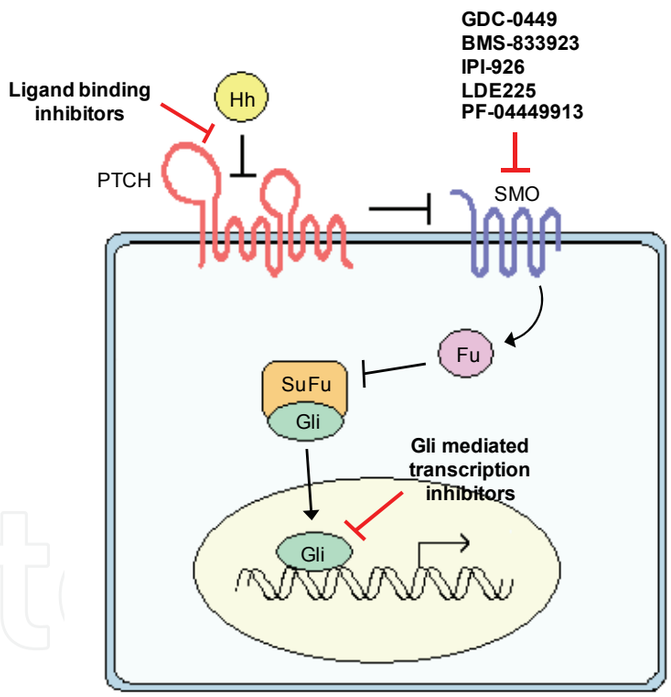

Fig. 2. Hedgehog signaling pathway.

In the absence of ligands, the receptor patched (PTCH) represses the smoothened (SMO) receptor. When the hedgehog (Hh) ligand is present, it represses PTCH which allows the serine/threonine kinase Fused (Fu) to induce the release of the transcription factor Gli from the sequestration by Suppressor of Fused (SuFu). Gli can therefore enter the nucleus and induce the transcription of target genes.

Molecules under study are being developed against the SMO receptor and against the processes of ligand binding and Gli mediated transcription.

Activation of SHH has been showed in basal cell carcinoma (BCC) of the skin (Hahn et al 1996; Bale and Yu, 2001), medulloblastome (Berman et al. 2002), pancreatic cancer (Berman et al. 2003; Kayed et al. 2004; Thayer et al. 2003), prostate cancer (Karhadkar et al. 2004; Fan et al. 2004), small cell lung cancer (Watkins et al. 2003), hepatocellular carcinoma (Sicklick et al. 2005; Patil et al. 2005) and also in hematological malignancies (Kubo et al. 2004)

Therapeutic inhibition of the Hh signaling destroys CSC, improves outcome, and even may effect a cure when is combined with gemcitabine in a direct pancreatic cancer xenograft model (Jimeno et al. 2009) suggesting the importance of combining therapeutic approaches that target CSCs with conventional drugs to improve efficacy.

Based on evidence, many inhibitors of this pathway are currently under development: (reviewed in Peukert and Miller-Moslin 2010) Although the majority of HH pathways inhibitors reported to date are SMO antagonist, drugs that block Hh ligand binding and GLI mediated transcription have been also been developed (see Figure 2, red arrows).

SMO inhibitors have already advanced to human clinical trials (reviewed in Peukert and Miller-Moslin 2010). GDC-0449 (RG3616) (Genetech) has already showed positive results in a Phase I study in patients with metastatic or locally advanced BCC (Von Hoff DD et al. 2009) that have led to an extensive clinical development as a single agent and in combination not only in BCC of the skin also in other tumor types such as colorectal, ovarian, breast, prostate, small cell lung cancer, pancreatic medulloblastoma and glioblastoma (http://www.clinicaltrials.gov/ct2/results?term=GDC-0449&pg=2).

Although less advanced in their development, other SMO inhibitors have already moved to the clinical setting: BMS-833923 (Exelixis/Bristol-Myers)
(http://www.clinicaltrials.gov/ct2/results?term=BMS-833923),
IPI-926 (infinity) (http://www.clinicaltrials.gov/ct2/results?term=IPI-926),
LDE225 (Novartis) (http://www.clinicaltrials.gov/ct2/results?term=LDE225), and
PF-04449913 (Pfizer) (http://www.clinicaltrials.gov/ct2/results?term=PF-04449913).

Wnt signaling pathway

The Wnt family of secreted glycoproteins also plays an important role in embryonic and adult stem cell biology and differentiation (reviewed Reya and Clevers, 2005). This pathway is considered as a master switch that controls proliferation versus differentiation (Van der Wetering et al. 2002) in both SCs and cancer cell maintenance and growth in intestinal, other epidermal and hematopoietic tissues (reviewed Reya and Clevers, 2005).

The Wnt pathway is subdivided into a so called canonical and a non canonical Wnt signaling. The canonical pathway (Figure 3) is the best understood and is dependent on the intracellular signaling molecule β-catenin (Cadigan & Nusse, 1997; reviewed in MacDonald, Tamai and He, 2009). The activity of the Wnt/β-catenin pathway is dependent of the amount of β-catenin in the cytoplasm. Normally the β-catenin level is kept low through continuous ubiquitin proteosome mediated degradation. In the "off state" of the pathway (absence of Wnt ligands), cells maintain low cytoplasmic and nuclear levels of β-catenin, although β-catenin is associated with the cell-cell adhesion molecule E-cadherin at the plasma membrane, an association that spares it from the degradative pathway. In the absence of Wnt ligands, cytoplasmic β-catenin is constantly degraded by the action of a destruction complex known as Axin composed by the Axin scaffolding protein, the adenomatous poliposys coli gene product (APC), casein kinase 1 (CK1) and glycogen syntase kinase 3 (GSK3). CK1 and GSK3 sequentially phosphorylate the amino terminal region of β-catenin allowing its subsequent ubiquitination and proteosomal degradation

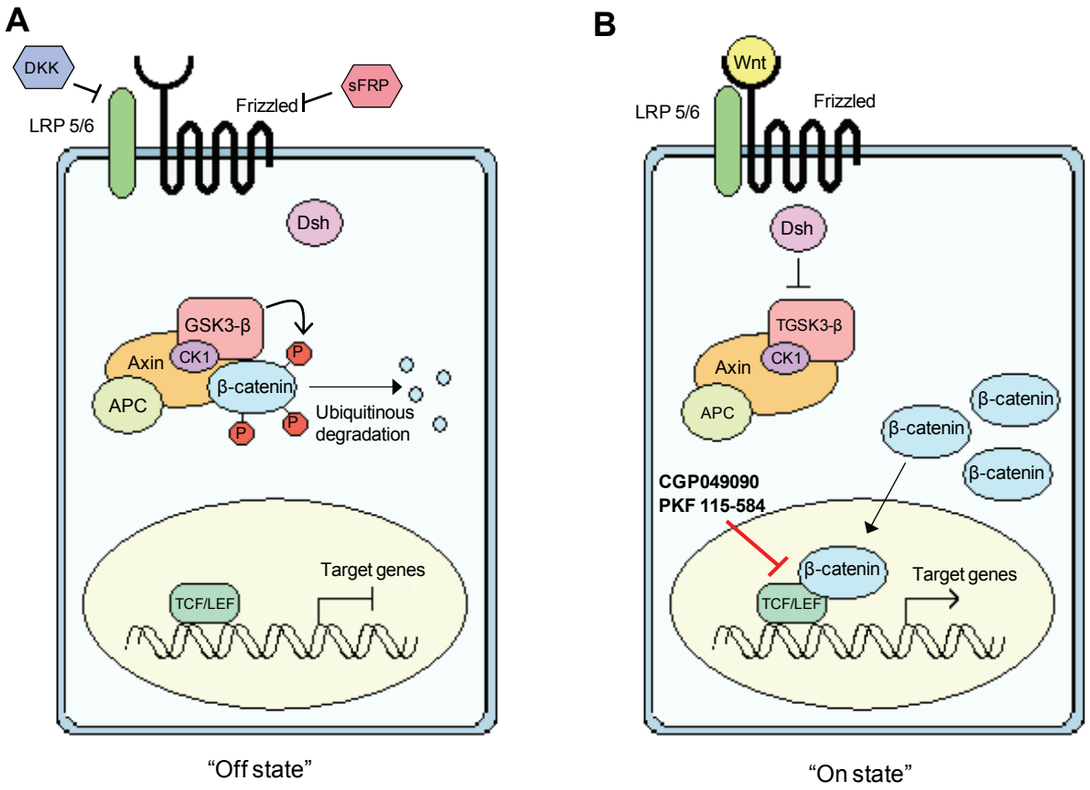

Fig. 3. Wnt canonical signaling pathway.
The "off state" of the pathway (A) takes place in absence of the Wnt ligand, The complex formed by Axin scaffolding protein, the adenomatous poliposys coli gene product (APC), casein kinase 1 (CK1) and glycogen syntase kinase 3 (GSK3) constantly induces the degradation of the molecule β-catenin due to a sequential phosphorylation that induces ubiquitination and proteosomal degradation which inhibits the translocation of β-catenin to the nucleus and transcription of target genes. In absence of β-catenin, T cell factor/ lymphoid enhancer factor (TCF/LEF) acts as a repressor of the Wnt target genes. Wnt antagonist such as Frizzled related proteins (sFRP) and Dikkopf (DKK) family members prevent the activation of the pathway.
On the "on state" of the pathway (B), Wnt binds to its receptor, Frizzled (Fz) and its co-receptor, the low density lipoprotein receptor related protein 5/6 (LRP5/6) inducing the activation of the phosphoprotein Dishevelled (DSH or DVL) and mediating the inhibition of the Axin destruction complex. The accumulation of β-catenin allows it to enter the nucleus and bind to TCF/LEF to activate transcription. Inhibitory molecules against the β-catenin/TCF interaction are currently under study.

(reviewed in MacDonald, Tamai and He, 2009). This degradation prevents the nuclear translocation of β-catenin and the subsequent expression of Wnt target genes. Thereby in absence of nuclear β-catenin, transcription factors such as DNA-bound T cell factor/ lymphoid enhancer factor (TCF/LEF) act as repressors of Wnt target genes instead of as activators (reviewed in MacDonald, Tamai and He, 2009) (Figure 3)

Activation of the pathway occurs when a Wnt ligand binds the transmembrane receptor Frizzled (Fz) and its co-receptor, the low density lipoprotein receptor related protein 5/6 (LRP5/6). In humans 19 members of the Wnt family and 10 Fz receptors have been described (reviewed in MacDonald, Tamai and He, 2009). This ligand-receptor-co-receptor interaction leads to the recruitment and activation of the phosphoprotein Dishevelled (DSH or DVL) that mediates the inhibition of the Axin destruction complex. Therefore, the on state of the pathway stabilizes cytoplasmatic β-catenin and allows its translocation to the nucleus where it forms a complex with TCF/LEF that leads to the expression of Wnt target genes involved mainly in cell proliferation (e,g c-myc, cyclcin D1, others) and in epithelial-mesenchymal transitions (EMT) (Figure 3). Secreted Wnt antagonist such as Frizzled related proteins (sFRP) and Dikkopf (DKK) family members prevent the activation of the pathway (Kawano and Kypta, 2003)

The non-canonical pathway is less understood and is also promoted by the Wnt Fz interaction but is apparently independent of β-catenin. Depending on the major intracellular mediator used it is called the Wnt/ jun N-terminal kinase (JNK) pathway or the Wnt/calcium pathway (reviewed in MacDonald, Tamai and He, 2009).

Aberrant Wnt signaling has been linked to a range of tumors. Elevated expression of some Wnt ligands and Dishevelled (DSH/DVL, a cytoplasmatic glycoprotein that acts downstream the Fz repceptor), loss of function mutations of APC or Axin and gain of function mutations in the amino terminal phosphorilation site of β-catenin has been associated with cancer (reviewed by Moon et al. 2004). Both mutations of β-catenin and APC genes are common in colorectal cancer (Kolligs et al. 1999). The APC gene is inherited or sporadic early mutated in the development of most colon tumors, which reduces the degradation of β-catenin (Van der Wetering et al. 2002). In non small cell lung cancer DSH/DVL genes are overexpressed (Uematsu et al. 2003). β-catenin accumulation has been also observed in breast cancer, melanoma, sarcoma, skin and brain tumors, and also hematological (myeloid leukemia and multiple myeloma) tumor samples (Reguart et al. 2005: Taipale & Beachy, 2001;Reya et al, 2003 ;Bastian et al, 2005; Mohinta et al, 2007; Bruxvoort et al, 2007). Furthermore, activating mutations in β-catenin have been found in endometrial (Okuda et al. 2010; Samarnthai et al. 2010), prostate (Robinson et al. 2008) and hepatocellular carcinoma (Whittaker et al. 2010) and an association of this pathway with renal cancer has been also suggested (Yamamura et al. 2010; Hirata et al. 2010)

Recently, two small molecular inhibitors, CGP049090 and PKF 115-584 (Novartis), both of them fungal derivatives, have been identified, which specifically disrupt nuclear β-catenin/TCF interaction (see Figure 3, red arrow) (Dihlmann and Von Knebel Doeberitz, 2005). These two compounds have already show anti-tumoral activity in acute myeloid leukemia cells (Minke et al. 2008), chronic lymphocytic leukemia cells (Gandhirajan et al. 2010) and in hepatocarcinoma cell lines (Wei et al. 2010) *in vivo* and *in vitro.*

Notch signaling pathway

Notch is a conserved signaling pathway that takes part in embryonic and postnatal development by regulating SC self renewal, cell fate specification and initiation of differentiation (reviewed in Bolós et al. 2007)

Four different Notch receptors (Notch 1-4) have been described in humans (Fleming, 1998). Each Notch gene encodes a single-pass transmembrane receptor that harbors an extracellular domain involved in ligand binding and a cytoplasmatic domain involved in signal transduction (Bolós et al. 2007).

There are also five Notch ligands in mammals, three Delta ligands and two Jagged ligands. These ligands are also membrane bound and they are placed in the surface of neighboring cells (Bolós et al. 2007)

Following the binding of the ligand, the receptor is activated by two consecutive proteolytic cleavages that lead to the release of its intracellular domain (NICD) (Figure 4). The first proteolytic cleavage is mediated by the metalloprotease ADAM17 (TNF-α-converting-enzyme or TACE), which cleaves Notch on the extracellular side, near the transmembrane domain. The released extracellular portion of the receptor is then transendocytosed by the cell expressing the ligand. The second cleavage occurs within the transmembrane domain and is mediated by a gamma-secretase activity whose key component is presenilin (Bolós et al. 2007). This final cleavage liberates the NICD, which subsequently translocates to the

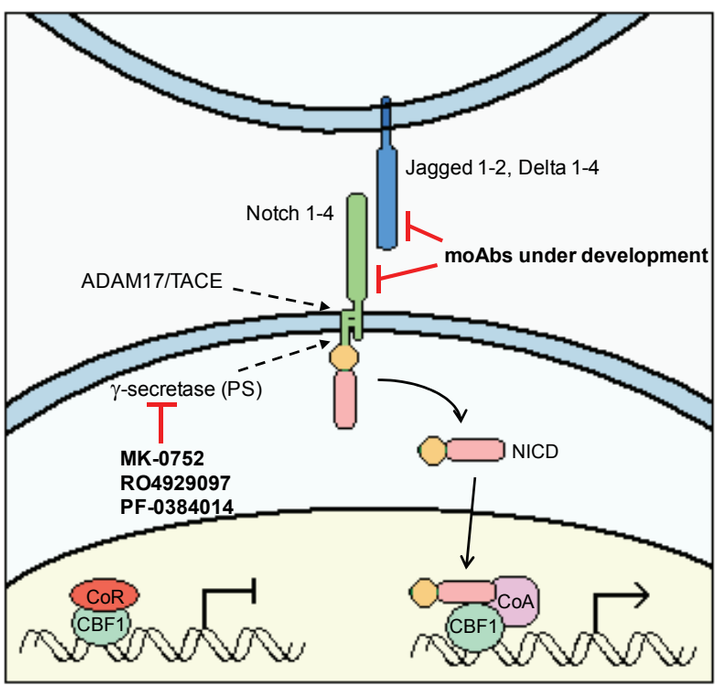

Fig. 4. Notch signaling pathway.

The binding of the Notch receptor (1-4) with its ligand Jagged (1-2) or Delta (1-4) placed in the surface of a neighbouring cell promotes the sequential cleavage of Notch by metalloprotease ADAM17 (TNF-α-converting-enzyme or TACE) and by a γ-secretase with presenilin (PS) as its key component. This cleavage liberates the NICD which translocates to the nucleus and binds to the transcription factor CBF1 displacing nuclear co-repressor proteins (CoR) and recruiting nuclear co-activator proteins (CoA) inducing the transcription of target genes.

Molecules against γ-secretase and monoclonal antibodies against Notch receptors and ligands are being developed to disrupt the Notch signaling pathway.

nucleus where it binds to the transcription factor CBF1. This interaction converts CBF1 from a transcriptional repressor into a transcriptional activator by displacing nuclear co-repressor proteins (CoR) and through the recruitment of nuclear co-activator proteins (CoA) (see Figure 4).

To date, only a few target genes have been identified; some of these genes are dependent on Notch signaling in all tissues, whereas others are tissue-specific (Bolós et al. 2007). The best-known Notch target genes are genes that encode for transcription repressors of the HES and HEY families. Genes that encode for Deltex1, the pre-T-cell receptor α and the cell cycle regulator p21 are also targets of NICD.

Deregulated expression of this pathway is observed in a growing number of hematological and solid tumors (Nickoloff et al. 2003). Aberrant Notch signaling may be necessary not only for the initiation of tumors but also for tumor maintenance (Weng et al, 2003; Roy et al,2007). Notch also has an important role in normal arteriogenesis and neo-angiogenesis, both of which are likely to be recapitulated in cancer (Rehman & Wang, 2006). In some instances, Notch signaling in endothelial cells appears to be triggered by ligands expressed on tumor cells (Zeng et al, 2005), which may contribute to the aggressive clinical behavior of those tumors expressing high levels of Notch ligands (Ridgway et al. 2006; Reedjik et a, 2005; Santagata et al, 2004; Bismar et al. 2006).

The result of alteration in Notch signaling seems to be dependent on its normal function in a given tissue (Radtke and Raj, 2003). In this context, Notch may act as an oncogene in those tissues where it is involved in stem cell self renewal or in cell fate decisions. On the contrary, Notch signaling may have a tumor suppressor role in those tissues in which Notch promotes terminal differentiation events (Radtke and Raj, 2003). Therefore, with the possible exception of keratinocyte derived tumors where Notch would have a tumor suppressor role, Notch signaling may be oncogenic in the rest of the tumors and its inhibition may be an effective strategy to combine with current therapeutic agents (Radtke and Raj, 2003).

An oncogenic role for Notch signaling has been suggested in breast and salivary gland epithelium (Jhappan et al. 1992; Weijzen et al,2002 la 38; Reedijk et al, 2005; Stylianou et al. 2006). The expression of Notch ligands such as Jagged1 correlates with a more aggressive disease course in both breast and prostate cancer (Reedjik et al, 2005; Santagata et al, 2004; Bismar et al. 2006). Loss of Numb, a negative regulator of Notch signaling, has been also observed in breast cancer samples (Pece et al. 2004) and has been associated with poor prognosis and chemoresistance (Colaluca et al. 2008)

Elevated levels of Notch receptors and their downstream targets are showed in primary human melanomas (Balint et al, 2005; Hoek et al, 2004), and enforced expression of constitutively active Notch1 promotes melanoma progression (Balint et al. 2005; Liu et al. 2006). Other neoplasias such as medulloblastoma (Marino et al. 2005; Hallahan et al. 2004), neuroblastoma (Ferrari-Toninelli et al. 2010) ovarian cancer (Park et al, 2006) and T acute cell lymphoblastic leukemia/lymphoma (T-ALL) (Weng et al. 2004; Aster, 2005) have an implication of Notch signaling in their pathogenesis.

Preclinical evidence suggest that Notch signaling may be involved in different breast cancer molecular subtypes and its inhibition may enhance the efficacy of current therapeutic agents (Rizzo et al. 2008; Osipo et al. 2008; Lee et al. 2008).A role for Notch signaling in intestinal SC biology is well established (Van Es et al. 2005; Fre et al. 2005)

Furthermore, a crosstalk between Wnt and Notch pathways has also been suggested in intestinal self-renewal and in the proliferation of adenomas and adenocarcinomas in the

intestine (Van Es et al. 2005). Gamma-secretase inhibitors enhanced the action of some chemotherapeutics in colon cancer cell lines (Van Es et al. 2005).
And monoclonal antibodies that target Notch receptors have also lead to an antitumoral effect in colon cancer models (Wu et al. 2010)
Notch signaling has also played an important role in hematopoiesis (Duncan et al. 2005). In fact, one of the clearest examples of oncogenic Notch signaling is found in T-ALL (Weng et al. 2004; Aster et al. 2005 ; Van Vlierberghe et al. 2006, Chiang et al. 2006). Less than 1% of T-ALL shows a chromosome translocation that leads to the expression of a constitutively active intracellular version of Notch1 (Weng et al. 2004; Aster et al. 2005) and more than 50% of human T-ALLs, without specific chromosome translocation, also show activating mutations in *Notch-1* (Weng et al. 2004; Aster et al. 2005) Furthermore, it has been shown that Notch1 also suppresses p53 function in T-ALL cells (Beverly et al, 2005) which could promote oncogenesis through increased cell survival and genomic instability.
A tumor suppressor role for Notch has been established in Keratinocyte-derived carcinomas (Rangaranjan et al. 2001; Nicolas et al. 2003) due to its role in differentiation events in the homeostasis of the skin (Lowell et al. 2000). The tumor suppressor effect of Notch in the skin may be mediated by its action as a repressor of the Hh and Wnt pathways in this tissue, both involved in self renewal of skin stem cells (Thelu et al. 2002; Devgan et al. 2005). The tyrosine kinase receptor of the epidermal growth factor (EGFR) also acts as a main player in skin tumorigeneis. EGFR has been also showed to be a negative regulator of *Notch1* transcription in keratinocytes (Kolev et al. 2008), also supporting a tumour suppressor role for Notch1 in the skin.
The molecular mechanisms by which aberrant Notch signaling causes cancer are not fully understood. Experimentally, Notch1 could collaborate with c-myc (Girad et al, 1996; Palomero et al,2006; Sharma et al,2006), E2A-PBX1 (Rohn et al, 1996) and Ikaros (Beverly & Capobianco, 2003), whereas Notch3 would down-regulate tumour suppressive E2A activity (Talora et al, 2003). Notch1 may inhibit p53-mediated apoptosis by stimulating signaling through the PI3K-Akt-mTOR-eIF4E pathway (Mungamuri et al, 2006), and may antagonize the growth suppressive effects of the transforming growth factor beta (TGF-β) signaling pathways (Sun et al, 2005). Other researches suggest the existence of an intimate and functionally important interaction between Notch and hypoxia-inducible factor (HIF)-1α, a transcription factor that regulates many genes involved in the response to hypoxia, including factors that promote angiogenesis (Gordan & Simon, 2007). Other data suggest that HIF-1α binds and stabilizes activated Notch1, leading to enhanced Notch signaling (Gustafsson et al, 2005). Expression of HIF-1α and Notch1 are correlated in breast cancer, in which Notch1 appears to up-regulate HIF-1α expression (Soares et al, 2004). It is also possible that Notch ligands on tumor cells impact the host immune response through effects on B and T cells (Dallman et al, 2005)
Based on the role of Notch signaling in the homeostasis of adult tissues and its implication in cancer, gamma secretase inhibitors (GSIs) and monoclonal antibodies against Notch receptors and ligands are under development (see Figure 4, red arrows) by large pharmaceutical companies as a new therapeutic tools (Reviewed by Miele et al. 2006).
MK-0752 (Merck) is a GSI under clinical development in early stage and advanced breast cancer, stage IV pancreatic cancer, recurrent or refractory CNS cancer and T-ALL (http://www.clinicaltrials.gov/ct2/results?term=MK-0752). RO4929097 (La Roche) is another potent GSI (Luistro et al. 2009). Numerous Clinical trials with RO4929097 are underway in brain and CNS tumors; breast; colorectal; kidney; lung; melanoma; ovarian

and pancreatic (http://www.clinicaltrials.gov/ct2/results?term=RO4929097). PF-0384014 (Pfizer) is also a GSI that have already shown antitumor and antiangiogenic effects in preclinical breast cancer models (Zhang C et al AACR 2010). A clinical trial in advancer solid tumors and in leukemia patients is underway with this drug (http://www.clinicaltrials.gov/ct2/show/NCT00878189?term=notch&rank=17).

4. Conclusions

Conventional chemotherapy and even new anti-target agents for the treatment of cancer patients in advanced stages have only yielded limited benefit in overall survival.
If a small but long lived population of tumor cells, CSCs, is involved in resistance and relapse to current anti-cancer therapies it seems of paramount importance to understand the molecular events governing these CSC in order to develop therapies specifically aimed at them.
At the moment, drugs that can block pathways considered critical for the maintenance of stem cells are under clinical development. The future will tell us if thanks to these new drugs there will be a turning point in the treatment of cancer.

5. Abbreviations

SC – stem cell
CSC – cancer stem cell
Shh – Sonic Hedgehog
Wnt – Wingless
Hh – Hedgehog
HIF - Hipoxia inducible factor

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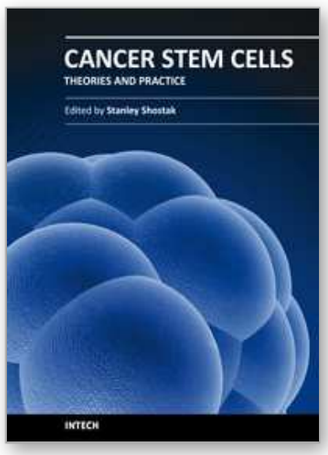

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