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Towards New Anticancer Strategies by Targeting Cancer Stem Cells with Phytochemical Compounds

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1. Introduction

Cancer stem cells (CSCs) are believed to be responsible for tumor initiation and development, metastasis and resistance to radio-therapy and *a priori* to numerous natural or synthetic chemical compounds. A large body of observations support now the 100 year old hypothesis which predicted a clonal genetic background of the heterogeneous cell population found in a tumor outgrowth [Paget, 1889]. Accordingly, since Dick's laboratory pioneering work in 1994 [Lapidot et al., 1994], growing realizations suggest that CSCs arise from embryonic, fetal or adult stem cells (SCs) or closely related dedifferentiated descendants. Interestingly, the concept that CSCs give rise to the bulk cancer cells is in accordance with the germ theory of disease developed by Koch in the 19th century [Garcion et al., 2009]. This theory points out that any disease has a unique causative agent. Although Koch's dogma suggests that tumors should arise from CSCs, it must also be borne in mind that their descendant cancer cells can generated dedifferentiated cells with a parental phenotype and therefore can be involved in the outburst of a secondary cancer.

On the basis of epidemiological data, it has been recurrently reported that diet rich in fruits and vegetables has cancer-protective properties; this suggests that plant-derived compounds are able to restrict the expansion of CSCs and even to kill them. The chemotherapeutic benefits of different natural or synthetic phytochemical agents on cancer cells are well documented. However their effects on CSCs are poorly understood, to a large extent because on the absence of well characterized experimental models. The objective of this chapter is therefore to recapitulate some aspects of the biology of CSCs and to propose different cellular tools and molecular preys for thorough pharmacological studies on CSCs, on the basis of the most recent data concerning the stemness factor Oct4. After reviewing known effects of specific phytochemicals on CSCs, we will focus on related promising strategies which could target the Achilles' heel of CSCs, in particular those harboring a selective sensitivity to oxidative stress and/or present in weakly differentiated Oct-4 expressing cancers.

2. Overview of cancer stem cell biology

2.1 Properties of cancer stem cells

CSCs share many characteristics with SCs and can be defined by their capacity to undergo self-renewal and to differentiate into more or less restricted cell types (from pluripotency to monopotency), depending on their embryological origins. The ability to self-renew allows the expansion of either the SCs or CSCs pool, in response to controlled or uncontrolled systemic and local signals respectively. Cell self-renewal involves either an asymetric or a symetric division process and allows the production of two daughter cells, one being identical to the mother cell and the second being expected to lose some of its lineage-specific competencies [Morrison & Kimble, 2006]. Actually differentiation from the SC or CSC compartment involves a sequential production of cells with more and more tissue-specific spezialization [Lobo et al., 2007; Sell, 2004]. Interestingly the level of aggressiveness of the CSCs seems to be related to their state of differentiation; poorly differentiated cells are highly aggressive while nearly terminally differentiated cells only give rise to benign tumors (Fig. 1). Since the fine balance between proliferation and differentiation is expected to be corrupted in CSC, it can be hypothesized that the biological chaos will be even more pronounced when a CSC exhibits a higher proliferation rate for a longer retention time until its final differentiation.

In view of its properties, a CSC can be firmly distinguished from a cancer cell by its unique capacity to undergo differentiation. However both of these cell types have enhanced growth ability which can be closely correlated with elevated levels of glycolysis and increasing metabolic activity. This property, previously described by Warburg, is considered as one of the most fundamental alterations occurring during malignant transformation [Warburg, 1924]. Adversely it has been postulated that a given CSC could originate from a cancer cell (or a CSC with lower lineage-specific competencies) which dedifferentiates into a stem-like cell (or into a CSC with higher lineage-specific competencies). Although dedifferentiation has not yet been identified as a naturally occurring process, an increasing number of reports assume the concept of such oncogene-induced plasticity [Rapp et al., 2008; Visvader, 2011], recently validated by mathematical modelings [Leder et al., 2010].

2.2 Regulatory networks of cancer stem cells in the niche

Accumulating evidences have shown that CSCs, like SCs, are regulated by common molecular pathways. Wnt/beta-catenin, Notch and Hedgehog pathways have been shown to be involved in the self-renewal regulation of both SCs and CSCs [Blank et al., 2008; Lobo et al., 2007]. In particular, Wnt signaling is known to promote proliferation of SCs when it binds its receptor Frizzled; a negative signal is then sent to inhibit the activity of APC (Adenomatous Polyposis Coli) which controls the degradation of beta-catenin. Increased amount of stabilized cytoplasmic and consequently nuclear catenin triggers then cell growth. Accordingly, accumulation of beta-catenin has also been frequently reported in various cancer cell types [Reguart et al., 2005]. Mice expressing constitutively activated beta-catenin showed highly proliferative tumors. Nevertheless apart their incidence on SC/CSC proliferation, an impaired activity of Wnt, Notch and/or Hedgehog pathways should also interfere with SC/CSC competency and its differentiation capacity. Indeed the balance between proliferation and differentiation for a proper self-renewal is difficult to determinate, as observed for example by the dual role of Wnt in both cell processes. A growing body of reports suggests that Wnt signaling can provide instructive signals that change the

commitment of SCs [Angers & Moon, 2009]. Given that different Wnt and Frizzled proteins can lead to the activation of either a catenin-dependent or -independent pathways, it seems obvious that these latter could somehow influence the cell fate of both SCs and CSCs.

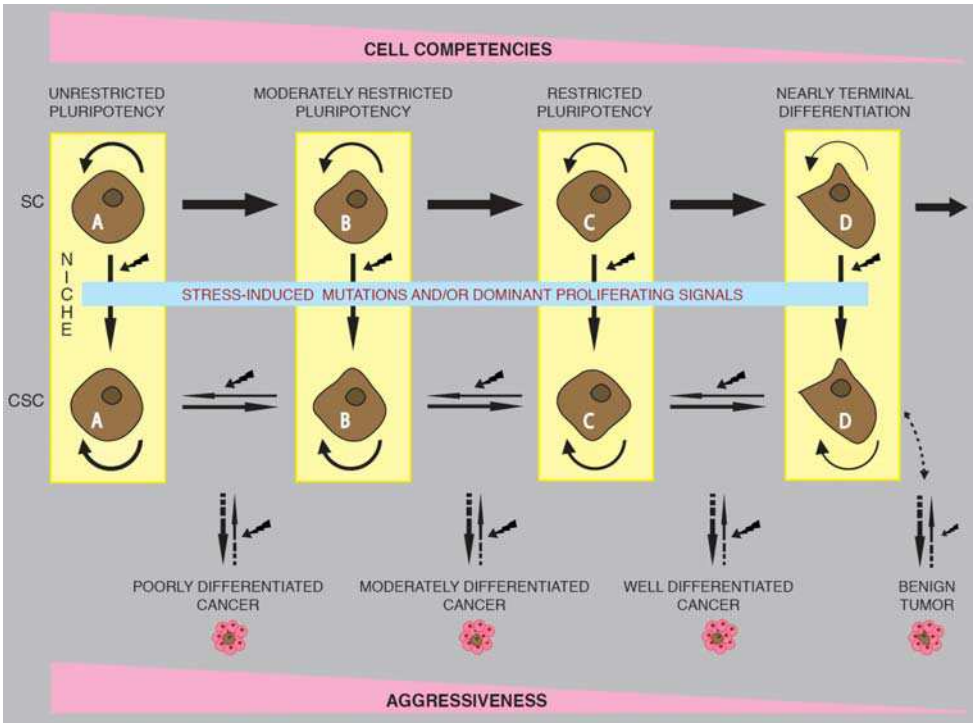

Fig. 1. Hierarchical and dynamical relationships between SCs, CSCs and their descendants. By successive differentiation waves, SCs lose step by step their cell competencies and become highly specialized cells. Stress-induced mutation and/or dominant proliferating signals trigger the transformation of SCs, committed to a specific fate, into CSCs which share the same differentiation profile. Uncontrolled proliferation of their homeless descendants leads to the outburst of a tumor which malignancy depends upon the differentiation stage of the tumor-initiating cells. Additional oncogenic hit likely allows CSC descendants to dedifferentiate into cells which possess higher lineage-specific competencies. The different types of SCs (and their corresponding CSCs) harbor distinct phenotypic markers (depicted by A to D) and show differential self-renewal capacity (depicted by faint to thick semi-circular arrows)

CSCs, in contrast to SCs, are not able to control their own population size. This suggests that the homeostatic regulation of CSCs by the niche is impaired. Indeed SCs are known to be anchored to niches found in a limited and specialized microenvironment of the different organs in the body (Fig. 1). Usually these cells are quiescent and are devoted for replenishing dead cells and repairing damaged tissues ; however SCs may be transformed in activated CSCs when exposed to repetitive mutation-inducing stress injuries without any ability to escape throughout the cell flux or to undergo apoptosis. Leaving their dormant

state, CSCs poised by failures of the self-renewal system and unable to respond in an appropriate manner to Wnt, Notch or Hedgehog signals, may then proliferate without restraint and escape from the niche, leading to the outburst of the tumor. However it has also been hypothesized that alteration of the niche by dominant proliferation-promoting signals could explain why SCs lost the dependance for limited expansion and become uncontrolled with a higher risk of oncogenic drift [L. Li & Neaves, 2006]. Thus restoring the regulatory signaling pathways in the niche might be a promising strategy to keep CSCs in check.

2.3 Models for studying cancer chemoprevention: identification of CSC markers

A direct consequence of the existence of CSCs assumes that future anticancer treatments should target this cell population. It is therefore critical to better characterize them. Some markers, like the cell surface antigen CD133, have been recommended for a prospective isolation of CSCs (Table 1). However recent studies have indicated that CD133 is also expressed in differentiated normal cells of various organs and CD133-negative cancer cells can also initiate tumors [Salnikov et al., 2009]. In this point of view, a very convincing report has clearly shown that a hierarchy of self-renewing CSC types expressing or not CD133 can be identify in glioblastoma tumors [Chen et al., 2010]. Therefore the relative reliability of such markers in CSCs, and consequently the absence of *bona fide* CSCs lines, remains a main barrier for studying the effects of potential cancer chemopreventive agents. For that purpose, commonly used chemical carcinogens were also used to initiate tumors of specific cell types; moreover the question of interlaboratory variability and standardization still remains

Tissue	Marker	Description	Reference
Brain	CD133 (Prominin 1)	Transmembranic	Prestegarden & Enger, 2010
Breast	CD44 (Homing Cell Adhesion Molecule)	Transmembranic	Garvalov & Acker, 2011
Colon	CD24 (Heat-Stable Antigen)	GPI-anchored	Todaro et al., 2010
Ovary	CD117 (c-Kit)	Transmembranic	Garvalov & Acker, 2011
Pancreas	CD326 (Epithelial-Specific Antigen –ESA-)	Transmembranic	C. Li et al., 2009
Prostate	Prostate Stem Cell Antigen (PSCA)	GPI-anchored	Saeki et al., 2010
Testis	CD9 (Tetraspanin 29)	Transmembranic	Biermann et al., 2007

Table 1. Frequently recommended cell surface marker for the detection and isolation of CSCs in various tissues. Some additional markers are routinely used to purify CSCs to homogeneity (Keysar & Jimeno, 2010), like CD44 for colorectal cancer or CD133 for breast carcinoma. It should be noticed that CD44 is recurrently mentioned as a reliable marker of any type of CSCs. Moreover the marker expressed in tumor-initiating cell denotes more precisely the embryonic origin of the cell than the tissue where it developped [Visvader, 2011]. GPI: glycosylphosphatidylinositol. (Prestegarden & Enger, 2010)

to be solved [Rosenberg et al., 2009]. Within the framework in this debate, embryonic stem cell lines (and their malignant counterparts, the embryonal carcinoma stem cell lines) are expected to be suitable models of CSCs and can be used as surrogated investigational tools for thorough evaluation of potential anticancer chemopreventive agents. Accordingly, numerous available teratocarcinomal cell lines were obtained after serial xenotransplantation and cultivation; such experimental design allows the recapture of the malignant phenotype and is widely used to isolate CSCs from any tumor tissue [Sell, 2004].

2.4 The Oct4 mystery

2.4.1 Regulation of Oct4 expression in stem cells

Oct4 (also known as POU5F1), a member of the POU-domain family of transcription factors, plays an essential role in the maintenance of embryonic stem cell potency and the establishment of the germ cell lineage. In embryonic stem cells, an Oct4 expression level between 50% and 150% of the endogenous amount appears to be permissive for self-renewal and maintenance of cell potency. Oct4 is downregulated during gastrulation when SCs differentiate, and eventually its expression is confined to the germ cell lineage. Consistent with its expression profile, it has been shown that Oct4 is active in embryonic stem cells, embryonal carcinoma cells and embryonic germ cells (Fig. 2). Upon treatment with retinoic acid (RA), these cells differentiate and Oct4 is rapidly downregulated [Pesce & Schöler, 2001].

Finely tuned functional Oct4 levels are crucial for phenotype stability and it is believed that the induction or repression of Oct4 is heavily regulated in order to avoid any deleterious effect of a transient dysfunction. It has been shown that the regulation of Oct4 expression involves different members of the nuclear receptor superfamily, including SF-1 (Steroidogenic Factor 1), LRH-1 (Liver Receptor Homolog-1) and GCNF (Germ Cell Nuclear Factor) [Kellner & Kikyo, 2010]. By means of genetic, molecular, and pharmacological studies, a recent report has demonstrated that a catenin-dependent LRH-1 regulation is required for maintaining steady-state levels of Oct4 [Wagner et al., 2010]. This means that the balance between proliferation and differentiation of pluripotent SCs involves, at least in part, a Wnt/beta-catenin control which can specifically target the upstream regulators of the stemness factor Oct4. Moreover it has been argued that GCNF is able to recruit different MBD (Methylated CpG Binding Domain) proteins to the Oct4 promoter, suggesting a link between Oct4 gene repression and its epigenetic locking [Gu et al., 2006]. A cascade of events from the binding of extracellular signaling molecules to Oct4 gene silencing can therefore be outlined. However additional as yet unknown mechanisms of regulation might also emerge in the future.

MicroRNAs (miRNAs) are known to regulate posttranscriptionally a target, by pairing with a short antisense stretch located in the 3′-untranslated region of its mRNA, in order to affect its stability and/or translation. A recent report has shown that miR-145 binds to Oct4 mRNA, represses its expression and induces lineage-restricted differentiation of embryonic SCs [N. Xu et al., 2009]. Intriguingly, three other miRNAS, *e.g.* miR-134, miR-296 and miR-470, have been described to target in the amino acid coding sequence of Oct4 mRNA, leading to transcriptional and morphological changes of the pluripotent SCs [Tay et al., 2008]. Theses observations demonstrate therefore that the levels of Oct4 can be indirectly regulated by different naturally occurring miRNAs and that these latter can induce a phenotypic switch of SCs from a highly pluripotent to a more restricted state.

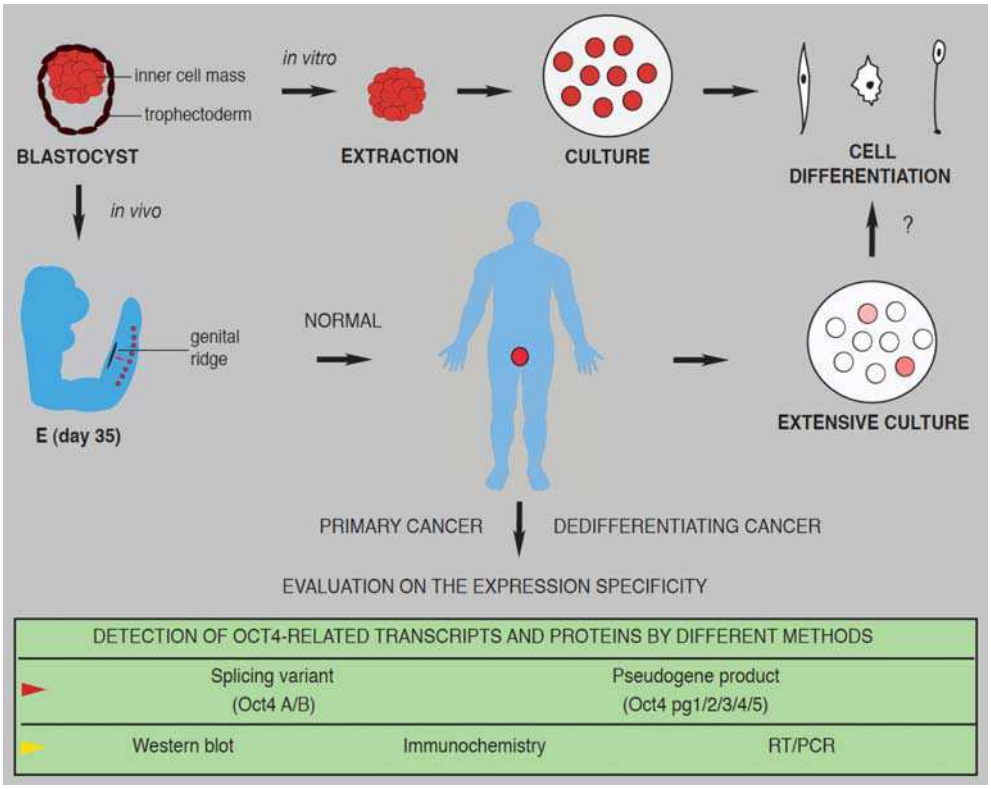

Fig. 2. Recapitulation of *in vivo* and *in vitro* expression of Oct4-related proteins in human SCs and CSCs. Oct4 is highly expressed in the inner cell mass of the blastocyst; at day 35 of the embryonic development, the expresion of the protein is confined in the germ cells, which will later on invade the genital ridges. Cultivated embryonic stem cells from the blastocyst give rise to different cell types which do not express Oct4. Extensively cultivated somatic cells might express Oct4 to a limited extent, but their ability to acquire stem-like properties remains questionable. An Oct4 signature can be identified in numerous cancer cells; depending upon the experimental method used, the detectable expression of Oct4 splicing variants and/or pseudogene products might be artifactitious or specific of some types of CSCs, and therefore could be involved in the etiology of the neoplasia. The role of Oct4 homologs (*e.g.* Oct1) should also be considered. Oct4 is depicted in red; the brightness of the color represents the amount of expression

Oct-4 transcriptional activity is regulated at the posttranslational level by different mechanisms. Sumoylation by SUMO-1 (Small Ubiquitin-related Modifier, 1) increases the stability of the protein and its transactivation potential [Wei et al., 2007]. In contrary, its ubiquitination by the E3 ubiquitin-protein ligase WWP2 (WW domain-containing Protein, 2) promotes its degradation [H. Xu et al., 2009]. Finally the repression of Oct4 expression, at the transcriptional, posttranscriptional and now posttranslational level [Shi & Jin, 2010], implicates multiple regulators which might be potential targets for a selective ablation of Oct4 function. This issue will be specifically addressed in the last section.

2.4.2 Oct4-dependent transcriptional networks in stem cells

As a major guardian of early stemness preservation, Oct4 regulates the transcription of numerous genes to maintain the self-renewal and pluripotency properties of the embryonic stem cells (Table 2). The POU factor interacts via its two domains POU and Hox with the octamer motif ATGCAAAT (or certain variants) located at the promoter(s) and/or the regulatory regions of the different target genes [Pesce & Schöler, 2001]. By this way, Oct4 activates or represses genes which are associated with proliferation and differentiation processes. Through ChIP-on-chip analysis, more than 900 putative direct downstream targets of Oct4 have been identified [Jung et al., 2010].

Target gene	Protein function	Cell process	Reference
CDX2 (caudal type homeobox transcription factor 2)	Transcription factor	Differentiation induction	Babaie et al., 2007
FGF4 (fibroblast growth factor-4)	Signaling molecule	Differentiation repression	Chew et al., 2005
nanog	Transcription factor	Stem cell identity	Rodda et al., 2005
NDUFA3 (NADH dehydrogenase [ubiquinone] 1 alpha subcomplex, 3)	Mitochondrial electron carrier	Cell metabolism	X. Chen et al., 2008
Oct4	Transcription factor	Stem cell identity	Chew et al., 2005
p21 (WAF1 ; CIP1)	Cyclin-dependent kinase inhibitor	Proliferation inhibition	Lee et al., 2010
SOX2	Transcription factor	Stem cell identity	Chew et al., 2005
TP53 (p53)	Tumor suppressor	Cell death	Campbell et al., 2007
SUZ12 (suppressor of zeste 12 homolog)	Polycomb repressive complex 2	Chromatin remodeling	Sharov et al., 2008

Table 2. Representative set of genes targeted by Oct4. The above mentioned downstream effectors of Oct4 were selected on the basis of experimental evidences, mainly involving functional genomic analysis after loss of Oct4 function. Note that *nanog*, *Oct4* and *SOX2* are also transcriptionally regulated by Oct4, pointing out the crucial role of the POU factor in the maintenance of a stemness profile in embryonic stem cells. By targeting genes involved in cell growth and differentiation, Oct4 enables an efficient and proper self-renewal of undifferentiated cells

To achieve a higher specificity, Oct4 may form protein complexes with other transcriptional regulators, including the homeobox protein nanog and the SRY-related HMG-box protein SOX2. Indeed large-scale mapping studies interrogating the binding sites of these three transcription factors showed their co-occupancy on distinct sets of target genes, suggesting

that their assembly in multiprotein complexes could serve as a mechanism for directing specificity by regulating stem cell-related gene expression [Boyer et al., 2005].
Interestingly, a growing body of observations highlights new insights about Oct4 activity in SCs and particularly in embryonic stem cells. Some candidates transcriptionally regulated by Oct4 are miRNAs. As an example, the POU factor binds to the promoter region of the miR-302 cluster in pluripotent cells, inducing an transcriptional activation of the miR-302s and the translational repression of its corresponding targets, such as the cell cycle regulator cyclin D1 [Card et al., 2008]. Interestingly miR-302 members are predicted to target many cell cycle regulators, suggesting that Oct4 could indirectly be implicated in the control of the different cell cycle checkpoints. More recently, it has been shown that Oct4 regulates the expression of miR-106b family members which target *p21* mRNA at its 3′ untranslated region and thus indirectly p21 levels [Koster et al., 2010]. These observations first suggest an unconventional supplementary link between Oct4 and cell cycle regulation in highly undifferentiated SCs. It can also be expected that in the future an increasing number of miRNA genes might be identified as targets of Oct4.

2.4.3 Oct4-related proteins in stem cells and cancer stem cells

The human *Oct4* gene comprises five exons. Two isoforms generated by alternative splicing, namely *Oct4A* and *Oct4B*, have been identified. Both have identical DNA-binding domains and C-terminal transactivation domains. Oct4A (*i.e.* Oct4) is localized in the nucleus while Oct4B is mainly localized in the cytoplasm and therefore should not be able to sustain self-renewal [Cauffman et al., 2006; Lee et al., 2006]. On the other hand, five different pseudogenes (numbered *Oct4-pg1* to *Oct4-pg5*) have been evidenced by whole-genome analysis and are highly homologous to the parental *Oct4* gene [Pain et al., 2005]. In view of their structure, these pseudogenes can theoretically be transcribed and translated and therefore could participate unexpectedly in some physiological or physiopathological processes. The plethora of Oct4 isoforms and *Oct4* pseudogene products should therefore be carefully taken in account when a putative Oct4 signature is expected to be detected in a specific type of SCs or CSCs (Fig. 2). Recently some *in vivo* studies have reported the detection of the stemness factor Oct4 in a variety of somatic tissue-derived cells, but these observations seem to be related to experimental pitfalls. However it cannot be excluded that somatic cells cultured for extensive periods of time could reactivate Oct4 function [Lengner et al., 2008]. The discussion that this reflects or not physiological processes to maintain somatic SCs in a self-renewal mechanism is still open.
Although the transcription factor Oct4 is known to be essential for pluripotency maintenance and self-renewal, its expression in putative CSCs, like that of CD133, remained controversial in the past years [Liedtke et al., 2008]. However growing body of evidences support now the idea that Oct4 could be expressed in CSCs from diverse tumor origin [Kang et al., 2009]. Oct-4 expression is clearly associated with bladder carcinogenesis [Atlasi et al., 2007] and germ cell malignancy [Cheng et al., 2007]. It should be noted that, as nongerminomatous germ cell tumors, embryonal carcinomas and their derived cell lines, are therefore expected to be suitable experimental models for studying the biology of Oct4-positive CSCs. Similarly a pluripotency gene expression signature has been evidenced in poorly differentiated and highly aggressive cancers [Ben-Porath et al., 2008]. Since this stemness identity involves Oct4 and its two coregulators, *e.g.* nanog and SOX2, it can be assumed that the regulatory networks controlling the activity of SCs are also functional in some cancers. Interestingly, the three proteins seem to be present even in far developmentally

related adult tumors, suggesting that the bulk cancer cells were able to dedifferentiate to a less restricted competency state.
Intriguingly, it has been shown that breast carcinoma and glioma can express *Oct4* pseudogenes; however it seems that their products lack Oct4-like activity on the basis of their absence of transcriptional activation potential on known Oct4-responsive luciferase constructs [Zhao et al., 2011]. This suggests that the detection of *Oct4* pseudogenes could have led to misinterpretation of some previous studies claiming the presence of Oct4 in CSC subtypes. Further investigations are thus necessary in order to address this issue and to solve whether Oct4 splicing variants and pseudogene products might be involve in SC identity and in the etiology of certain cancers (Fig. 2). Moreover a possible role of some Oct4 homologs in the induction of the neoplasic process has been recently emphasized; Oct1, like Oct4, binds to the same DNA sequences, regulates common target genes and are under the control of identical upstream regulators. It is therefore hypothesized that Oct1 or other Oct proteins might carry out similar malignancy functions as Oct4 [Kang et al., 2009].

3. Phytochemicals and cancer stem cells

Epidemiological studies have consistently linked the intake of fruits and vegetables with reduced risk of initiation and development of cancer [Steinmetz & Potter, 1996]. Adversely, recent reports based on large propective studies downgraded the previous conclusions; the potential chemopreventive effects of diets rich in fruits and vegetables seem to be rather associated with healthy nutritional principles [Key, 2011]. However it is still believed that particular constituents in certain fruits and vegetables could have benefit effects. More than three-fourths of the anticancer compounds are either derived substances from natural products or the natural products themselves, mostly originating from herbal medicinal and dietary plants or from microbial sources. This section will therefore only focus on the cancer chemoprotective effects of some plant-derived compounds which chemical structure is known.
In a strict sense, phytochemicals with chemopreventive properties hinder the (re)appearance of a cancer by targeting CSCs, whereas phytochemicals with chemotherapeutic properties destroy a preexisting cancer by targeting cancer cells. However these latter can conceptually be considered, at least in part, as potential CSCs with very limited cell competencies (see Fig. 1). For that reason, chemotherapy and chemoprevention become hard to distinguish to each other, since they can theoretically target the cancer cell as well as the CSC. It is therefore not surprising that numerous plant-derived compounds might act on both cell types and have therapeutic and preventive effects [Aggarwal et al., 2004].

3.1 Targeting cancer cells by phytochemicals

3.1.1 Generalities

There is a plethora of *in vivo* and *in vitro* studies which have highlighted the benefits of phytochemicals against distinct cancer types. An exhaustive list of plant-derived compounds with known chemotherapeutic properties can be found elsewhere [Kawasaki et al., 2008; Shu et al., 2010]. By modulating multiple signaling pathways, they can target various cell processes, including induction of apoptosis as well as inhibition of cell survival, metastasis and angiogenesis. Such pleiotropic activity is for instance displayed by curcumin [Das et al., 2010]; this potent polyphenol antioxidant was originally extracted from tumeric, a spice made from the root of the plant *Curcuma longa* and which is widely consumed in the Indian

subcontinent countries. Curcumin is one of the most studied phytochemical compound and will be used as a referential model for the next issues.
It is worth noting that several plant-derived compounds are able to reverse the multidrug resistance (MDR) phenotype, usually observed in aggressive subpopulations of cancer cells. This pathological phenomena results from an intrinsic dysfunction of different energy-dependent transporter proteins (for example P-glycoprotein or member of the multidrug resistant-associated proteins) which are involved in drug entry and efflux [Molnár et al., 2010]. By down-regulating the expression of transporter proteins, some phytochemicals, like curcumin, can restore the chemosensitization in drug-resistant cancer cells [Limtrakul, 2007].

3.1.2 Molecular targets of apoptosis-inducing chemotherapeutic phytochemicals

Acquired resistance towards apoptosis is the key hallmark of all types of cancer [Hanahan & Weinberg, 2000]. Apoptosis is induced by both intrinsic (mitochondrial) and extrinsic (death receptor) pathways (Fig. 3). It is accompanied by successive biochemical events and morphological changes, like DNA condensation and fragmentation, cell shrinkage, membrane blebbing and membrane-associated apoptotic bodies [Saraste & Pulkki, 2000]. Curcumin is a very potent inducer of apoptosis and interferes with both the intrinsic and extrinsic proapoptotic signaling pathways; this phytochemical can therefore kill a wide variety of cancer cells, even if they exhibit some mutation(s)-induced failures in several steps of their proapoptotic machinery [Ravindran et al., 2009].
Apoptosis and cell survival are tightly associated in order to maintain cell population in a healthy homeostatic state. There are several points of crosstalk between the two operating systems. As a consequence, prosurvival signals increase the expression and/or the activity of antiapoptotic regulatory proteins, while repressing the expression and/or the activity of proapoptotic factors. At the opposite, proapoptotic signals activate the function of antisurvival molecules and inhibit the function of prosurvival factors. Such duality of action can be achieved because the two regulatory networks share common molecular targets. One of the most studied crosstalk between life and death signaling pathways is illustrated by the nuclear factor-κB (NF-κB). This DNA-binding protein participates in a dual role, wherein it mediates both prosurvival and proapoptotic signals. Actually the NF-κB pathway targets antiapoptotic and proapoptotic factors; depending upon the cellular context, its transcriptional competencies are modulated by specific upstream activators, like the serine/threonine protein kinase AKT or the FasL/TNF/TRAIL (Fas Ligand/Tumor Necrosis Factor/Tumor necrosis factor-Related Apoptosis-Inducing Ligand) death receptors [Jin & El-Deiry, 2005]. Such yin and yang connection can also be observed between the survival factor AKT and the tumor suppressor p53, or between NF-κB and p53 which competitively interact with the nuclear coactivators CBP/p300 (CREB-Binding Protein, related p300) and therefore reciprocally repress their activity [Dey et al., 2008].
Heat-shock proteins (HSP) are the significant integrators of the interconnective activity of the proapoptotic and prosurvival signaling networks. For instance, the chaperone protein HSP90 interferes with the function of several factors (*e.g.* p53) of the intrinsic and extrinsic apoptosis pathways, leading to cell death inhibition [Walerych et al., 2004]; HSP90 also promotes cell survival through its involvement in the formation of active NF-κB and the maintenance of AKT in its active phosphorylated form [Arya et al., 2007]. Taken together, all these findings might ultimately result in the development of highly efficient chemotherapeutic candidates which are able to target the upstream integrators, as well as several nodal points

of the pro-apoptotic and pro-survival machineries. In view of its widespread biological properties, curcumin should be considered; it is capable to disrupt HSP90 function [Wu et al., 2006], to upregulate p53 expression and to inhibit NF-κB and AKT activities [Ravindran et al., 2009]. However additional studies are needed to gain the full insights of the multifocal activity of curcumin and to identify the different proapoptotic and prosurvival crosstalk mechanisms that it can target.

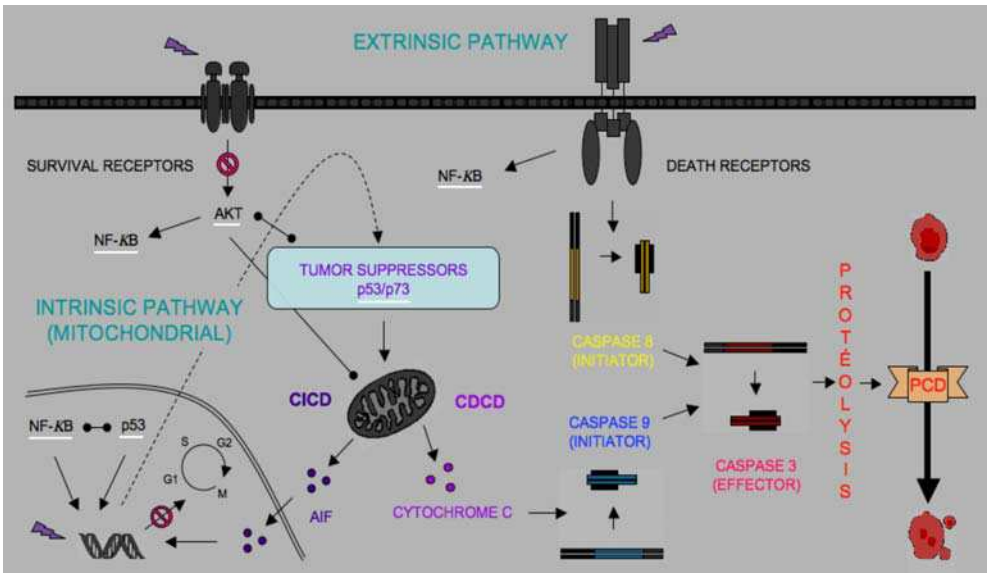

Fig. 3. Simplified scheme of the activity of a generic phytochemical on the different pro-apoptotic and cell survival-associated pathways. In response to a cellular stress generated by a phytochemical, two inter-connected proapoptotic pathways can be induced. The extrinsic pathway is initiated by an activation of the death receptors (Fas, TNF-R, TRAIL-R) and triggers a caspase 8-dependent apoptosis. The intrinsic signaling pathway is driven by the tumor suppressor p53 (or the p53-homolog p73), a main regulator of cell cycle progression; the DNA-damage induced activation of p53 initiates a caspase-independent (CICD) or caspase 9-dependent (CDCD) cell death process, associated with a mitochondrial release of either the chromatinolytic factor AIF (Apoptosis-Inducing Factor) or cytochrome C respectively. Finally the cleavage of pro-caspase 3 in its active subunits leads to proteolysis and programmed cell death (PCD). The functional repression of the survival receptors and their effectors, *e.g.* AKT and NF-κB, can also trigger apoptosis. It is worth noting that the death receptors are also implicated in the regulation of NF-κB pathway. HSP90, as an integrator of both cell survival and apoptotic activities, targets various factors (including those underlined in white); some of these factors repress each other's function (depicted by left right circle-headed arrow). The proposed phytochemical could be for instance curcumin (depicted by a zigzag arrow). Detailed relationships between the different factors can be found elsewhere [Jin & El-Deiry, 2005; Ravindran et al., 2009; Sarkar et al., 2009]. Note that failures of the intrinsic proapoptotic pathway can lead to an accumulation of DNA damages which in turn leads to incorrect DNA repair and mutations

Interestingly, induction of apoptosis triggers the suppression of the angiogenic process and the inhibition of tumor growth [Wang & Sun, 2010]. Moreover the signals that allow a migratory cancer cell to invade normal tissue, promote also cell survival by suppressing apoptosis [Stupack, 2007]. Therefore targeting cancer cells by apoptosis-inducing phytochemicals indirectly interrupt tumor neovascularization and metastasis. Accordingly curcumin has been shown to prevent angiogenesis and cancer cell invasion, thanks to its antiproliferative and proapoptotic activity [Kunnumakkara et al., 2008]. Finally, this phytochemical, by modulating the expression and activity of a wide variety of proteins, exhibits a strong therapeutic efficacy and could play an important role by cutting down cancer incidence. It should also be noted that this reductionist approach which only focuses onto two interconnected processes, namely apoptosis and proliferation and understates the other processes is theoretically valuable. Indeed it is expected that a normal cell should be corrupted by at least six different mutations to be convert into a cancer cell; these mutations are associated with self-sufficiency towards proliferative signals, insensitivity to growth suppressors, resistance for cell death, ability for limitless replication, angiogenesis induction and metastasis activation [Hanahan & Weinberg, 2000]. However the concomitant occurrence of multiple mutations in any cell is statistically rare if not impossible. This suggests that only one or two mutations, affecting selectively the proapoptotic or/and growth inhibitory potential, are necessary for the normal cell to initiate tumorigenesis [L, Li & Neaves, 2006]. As a fact, tumor-associated mutations in a single gene, *i.e. TP53*, are the main hallmark of most human cancers [Whibley et al., 2009]. In the light of the above considerations, it becomes clear that targeting the main actors of crucial processes, like apoptosis or cell survival, by a pharmacological agent remains one of the most effective strategy in anticancer treatment.

3.2 Targeting cancer stem cells by phytochemicals

3.2.1 Generalities

CSCs, like cancer cells, exhibit uncontrolled growth and therefore show quite similar susceptibility to plant-derived compounds, which should target, through their antiproliferative properties, common molecular pathways [Aggarwal et al., 2004]. Nevertheless it is expected that differentiation-inducing phytochemicals are able to counteract two different cell processes, namely the self-renewal maintenance which is specific of CSCs and the dedifferentiation drift which can affect both CSCs and cancer cells (see Fig. 1).

3.2.2 Targeting selectively cancer stem cells by apoptosis-inducing phytochemicals

A growing body of studies suggests that phytochemicals can trigger a proapoptotic response of potential or full-blown CSCs. For example, curcumin induces a decrease of the stem-like side population of the rat C6 glioma cell line, likely through a proapoptotic process [Fong et al., 2010]. Accordingly, curcumin activates the caspases of both the extrinsic and intrinsic pathways of apoptosis and represses AKT function (see Fig. 3) in various ovarian carcinoma cell lines [Watson et al., 2009], including the SKOV3 cell line from which a side population of CD133/CD117-positive cells (see Table 1) with cancer stem-like properties can be isolated [Ma et al., 2010]. The broccoli compound sulforaphane, a member of the isothiocyanate family of phytochemicals, represses NF-κB-dependent prosurvival activity of pancreatic CD44-positive tumour-initiating cells, leading to the downregulation of antiapoptotic proteins and induction of caspase activity followed by apoptosis [Kallifatidis et al., 2009].

The polyphenolic compound resveratrol triggers apoptosis by activating caspase-3/7 in pancreatic CD133/CD44/CD24/ESA-positive CSCs isolated from human primary cancer, suggesting that this pharmacological agent could be used for the prevention and treatment of pancreatic malignant tumor [Shankar et al., 2011]. In view of these examples, it can be expected that numerous phytochemicals, identified as proapoptotic agents on cancer cells, will also be recognized in the future as killers of CSCs. The main reason for this assumption is that various types of tumors and cancer cell lines, previously analyzed for their reactivity to plant-derived compounds, contain CSCs which self-renew and express SC markers [Kondo, 2007]. Therefore it is likely that the described sequence of pro-apoptotic events induced by a specific phytochemical in a given cancer cell should also be observed in its corresponding initiator. Such paradigm should notably be validated for plant-derived compounds, like polyphenols, which act as DNA damage inducers; the canonical molecular cascade usually implicates an activation of the p53 or p73-dependent cell cycle checkpoint signaling pathway and consequently an initiation of a caspase-mediated protein degradation and DNA fragmentation, leading to an irreversible growth inhibition by enhanced apoptosis [Narayanan, 2006]. Such sequence of events, shown in cancer cells, might also be evidenced in CSCs. If this extrapolation is confirmed, this would finally mean that apoptosis-inducing phytochemicals remain very powerful weapons against cancer since they target both CSCs and their descendants, hereby by common pathways.

Intriguingly some phytochemicals, in a reasonable range of concentrations, kill cancer cells without having any toxic effects on normal cells. This selectivity is poorly understood. Several explanations have been put forward. Most of tumor cells, in contrast to normal cells, constitutively express active NF-κB which mediates their survival [Prasad et al., 2010]. Phytochemicals with differential cytotoxic properties, like curcumin or the flavone wogonin, are known to repress the activity of NF-κB downstream targets [Li-Weber, 2009; Shishodia et al., 2005], thereby normalizing the exaggerated proliferation capacity of cancer cells and inducing their death. It is therefore tempting to think that all cancer cells exhibit a deregulation of NF-κB expression which could be selectively targeted by proapoptotic plant-derived compounds. However such cause-effect relationship has to be clearly demonstrated. Different mechanisms which lead to a constitutive expression of active NF-κB in cancer cells have been suggested, including dysregulation of cytokine receptors [Prasad et al., 2010]. Interestingly, it is known since the early 1990s that NF-κB is a redox-sensitive transcription factor; its activity is upregulated by enhanced levels of ROS (Reactive Oxygen Species) which are tighly associated with malignant initiation and progression. However several studies have shown that ROS has paradoxic effects on NF-κB activity, depending upon its levels. Mild increase of free radicals often induces NF-κB activation and sustained cell survival, while a drastic increase of free radicals leads to a repression of NF-κB function and cell death [Trachootham et al., 2008; Trachootham et al., 2009]. Actually, intracellular ROS production result from several processes, including the mitochondrial oxidative phosphorylation which involves a set of enzymatic complexes (*e.g.* NADH dehydrogenase, succinate dehydrogenase) constituting the respiratory chain. At the opposite, enzymatic antioxidants (*e.g.* superoxide dismutases, glutathione peroxidase) or scavengers (*e.g.* cystein, albumin) contribute to regulate the levels of oxygen-free radicals in order to protect the cells from oxidative damage and prevent mutation-induced malignancy. According to the oxidant and antioxidant mechanisms involved, changes in ROS levels can either directly impair the DNA binding capacity of NF-κB or trigger its transcriptional activity by promoting its nuclear translocation [Pani et al., 2010].

The redox status plays a crucial role in maintaining the cell activity under normal conditions. To reduce the risk of oxidative-induced mitochondrial apoptosis due to high proliferative-linked metabolic activity, cancer cells « adopt » a glycolytic state to the detriment of an oxidative state. This Warburg's effect leads cancer cells to maintain high levels of free radicals, in contrast to normal cells. Although CSCs similarly show enhanced ROS content compared to normal SCs, these two cell types produce only a limited amount of oxygen radicals, likely because they reside in a low oxygen microenvironment [Diehn et al., 2009]. This explains why some CSCs are resistant to radiotherapy and chemotherapic phytochemicals which require the availability of local oxygen to develop their cytotoxic activity. However the redox status and adaptation displayed by the CSCs and their descendants, as well as by their normal counterparts is a key mechanism that, to a certain extent, might explain the selective cytotoxic effect of a ROS-producing plant-derived compound. In regard to the crucial influence of redox homeostasis on the life-and-death processes, it was suggested that an additional and robust ROS-producing stress could kill the adapted but easily overwhelmed cancer cells, without having toxic side effects on normal cells [Fruehauf & Meyskens, 2007; Trachootham et al., 2008]. It can be postulated by extrapolation that CSCs, in contrast to normal SCs, harbor a similar weak adaptation capacity of the redox machineries when exposed to oxidative stress, induced for instance by a cytotoxic phytochemical. A hypothetical sequence of events can then be set forth to explain the selective effects of a plant-derived compound on cancer cells and CSCs (Fig. 4). However the molecular mechanism which leads to the quenching of the ROS buffering capacity has still to be identified. Limited adaptability of the redox homeostasis might be linked to some steric hindrance of factors involved in mitochondrial activiy. The absolute level of the redox balance in the normal and cancer cells (or their progenitors) might be the key parameter which needs to be considered for expecting a selective cytotoxic effect of a ROS-inducing pharmacological agent. Finally the higher sensitivity of some SCs to DNA damage-induced mutations has lead to cancer transformation and consequently to an adaptative redox response which might be easily and selectively overwhelmed by a prooxidant phytochemical. A redox-modulating strategy which targets the Achilles' heel of CSCs and their descendants could therefore have major implications in cancer treatment.

It is worth noting that a notable body of studies has highlighted the dual effects of some phytochemicals as antioxidants and prooxidants. As antioxidant agents, they are believed to protect DNA integrity by quenching oxygen-free radicals produced by a pathogenic oxidative stress and thus should impede the transformation of injured SCs. As prooxidant agents, they are able to kill CSCs and their descendants by triggering an intracellular production of ROS. These compounds, such as the polyphenolic flavonoids, are therefore acting as double-edged swords by targeting the redox regulatory system. The antioxydant or prooxidant effect of a particular phytochemical seems mostly to be dose- and time-dependent [Procházková et al, 2011; Schwartz, 1996]. The reason for this paradoxical activity of some plant-derived compound is still poorly understood. They could initially target a same ROS-sensing molecule which is involved in both antioxidant and prooxidant cell processes. The mitochondrial coenzyme Q could be such a candidate; this electron carrier is known to contribute to mitochondrial oxidative damage and antioxidant defenses [James et al, 2004]. However its precise role in the phytochemical-induced redox response of SCs, CSCs and their offsprings requires further studies.

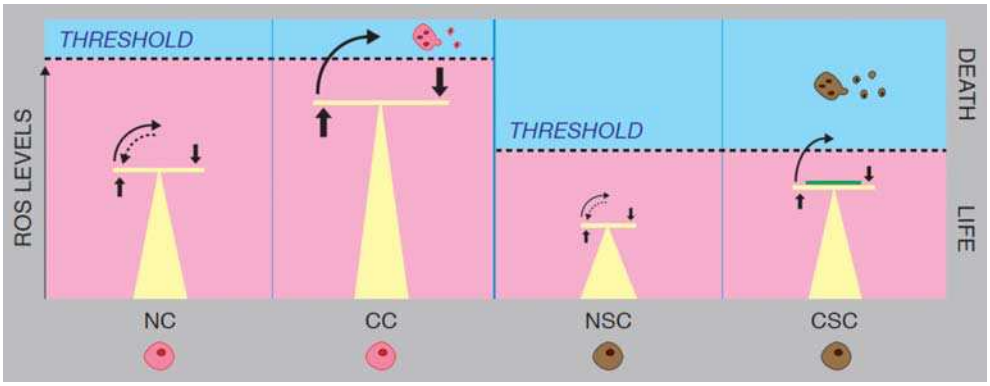

Fig. 4. Hypothetical effects of a selective cytotoxic prooxidant phytochemical on the redox homeostasis of normal cells, cancer cells and their respective progenitors. Normal cell (NC) and normal stem cell (NSC) are able to maintain low levels of intracellular ROS by controlling the steady-state activity of the oxidant and antioxidant machineries (depicted respectively by a left and right arm of a balance); both cell types can tolerate, in a reasonable range of concentrations, an oxidative stress (represented as a clockwise semicircle arrow) induced by a phytochemical (depicted by an upwards and/or downwards thick arrow pointing either one or the two arms of the balance) through adaptative antioxidant responses (represented as an dotted anticlockwise semicircle arrow). Cancer cell (CC) and cancer stem cell (CSC) show increased basal levels of ROS due to exaggered metabolic activity and are more vulnerable to further oxidative stress induced by a ROS-generating phytochemical. Enhanced production of oxidants overwhelms the antioxidant capacity of both cancer cells and CSCs which reaches a toxic biological limit (represented as a dotted horizontal line), leading to death. It is assumed that the death threshold is lower in NSC and CSC than in their corresponding counterpart, since they reside in an autarkic microenvironment which does not allow detoxication exchanges. CSC chemoresistance might be associated with a reorientation of the oxidant and antioxidant activities towards its initial levels (depicted by a green line on the top of the balance). Adapted from a previous review [Trachootham et al., 2009]

3.2.3 Targeting cancer stem cells by differentiation-inducing phytochemicals

3.2.3.1 Targeting the self-renewal pathways of cancer stem cells by phytochemicals

The aggressiveness of a CSC is proportional to its lineage-specific competencies (Fig. 1). Moreover several studies have reported that the differentiation level of a specific type of CSC is inversely correlated with its resistance capacity to radiotherapy and chemotherapy [Al-Hajj et al., 2004]. Therefore disrupting the molecular pathways which regulate CSC self-renewal is an attractive alternative for reducing the aggressiveness and MDR phenotype of the tumor bulk. By targeting these pathways, it is assumed that the CSC switches from a highly proliferative and undifferentiated state to a harmless low-growing and mature state. Accordingly, genes encoding proteins involved in Wnt/beta-catenin, Notch and Hedgehog signalings, are frequently mutated or aberrantly expressed in several fulminant cancers [Blank et al., 2008; Lobo et al., 2007]. Through direct or indirect modulation of the impaired

signaling pathway activities, plant-derived compounds are therefore expected to affect CSC self-renewal, leading to cancer regression and reduced risk of relapse. The most exhaustively studied differentiation-inducing pharmacological compounds are retinoids, including vitamin A and its derivatives. As an adjunct to clinical therapy, RA treatment allows complete remission of about 90% of patients with acute promyelocytic leukemia [Freemantle et al., 2003]. The anticancer activities of retinoids have been attributed, at least in part, to increased proteasomal degradation of beta-catenin, herein normalizing the aberrant activation of the Wnt signaling observed in some leukemias and solid tumors [Dillard & Lane, 2007; Mikesch et al., 2007]. This example highlights the strong positive impact of the differentiation strategy which is able to block the tumor burden. Actually, an increasing number of *in vitro* and *in vivo* studies show that various plant-derived compounds are potential anticancer agents since they can specifically target the self-renewal properties of CSCs [Kawasaki et al., 2008; Y. Li et al., 2011]. Moreover, links between different molecular components involved in the prosurvival and the self-renewal signaling pathways have been described in several reports, pointing out the fine-tuned balance which controls cell proliferation and differentiation [Konopleva & Jordan, 2011]. As a consequence, it is not surprising that some phytochemicals could act as multi-target agents by modulating the activity of specific nodal points of the prosurvival and self-renewal machineries [Sarkar et al., 2009]. All these issues will be discussed in details elsewhere (see Chapters 20 and 22).

Reprogramming of gene expression through epigenetic modifications could explain the prodifferentiating anticancer activity of plant-derived compounds. The Polycomb and Trithorax groups of proteins are known to reverse respectively active or repressed transcription states of developmentally important genes during SC fate commitment [Ringrose & Paro, 2004]. It is therefore expected that certain differentiation-inducing phytochemicals could disturb the activity of these epigenetic chromatin modifiers, leading transiently to an active resetting of the histone code and an erasure of DNA methylation. This assumption is based on the fact that at least two components of the Polycomb multiprotein complex, namely Bmi1 polycomb ring finger oncogene and SUZ12, have been shown to be direct effectors of Hedgehog and Wnt signaling respectively. As such, both proteins are implicated in SC self-renewal and known to be upregulated in different cancers [Galmozzi et al., 2006]. Although some naturally-occurring inhibitors of the hedgehog and beta-catenin signalings can regulate CSC proliferation and differentiation by modulating *a priori* the expression of Bmi1 and SUZ12, the discussion of a direct effect of a specific plant-derived compound on epigenetic chromatin modifiers is still open and needs further investigation. However several phytochemicals, including polyphenols, are able to target specifically several epigenetic alterations which might have led to cancer development. For instance, curcumin can reverse DNA hypermethylation and is suspected to reactivate methylation-silenced tumor suppressor genes in several colon cancer cell lines. Moreover curcumin, as a potent histone modifying compound, promotes the proteasome-dependent degradation of the histone acetyltransferase (HAT) p300/CBP in cell extracts from different cancer types. Such inhibitory effects is known to be associated with histone H3/H4 hypoacetylation and repression of HAT-dependent chromatin transcription, a hallmark of a highly proliferative and indifferentiated cell state [Link et al., 2010]. Plant-derived compounds seem therefore to be promising weapons against the epigenetic disorders which could affect cancer cells and CSCs. However due to data scarcity, an epigenetic reorientation strategy for an alternative anticancer therapy remains difficult to evaluate.

3.2.3.2 Targeting Oct4 function in cancer stem cells by phytochemicals

Targeting Oct4 network in poorly and aggressive Oct4-expressing cancers by phytochemical compounds is a very promising approach, in regard to its crucial role in stemness maintenance in both SCs and CSCs. On the other side, induced pluripotent stem (iPS) cell research could provide new insights into the mechanisms engaged during CSC differentiation. Indeed the current state of our knowledge in the field of cancer therapy and tissue engineering seems to indicate that CSC reactivity and somatic cell dedifferentiation share common molecular pathways in which Oct-4 could play a pivotal role (Fig. 5).

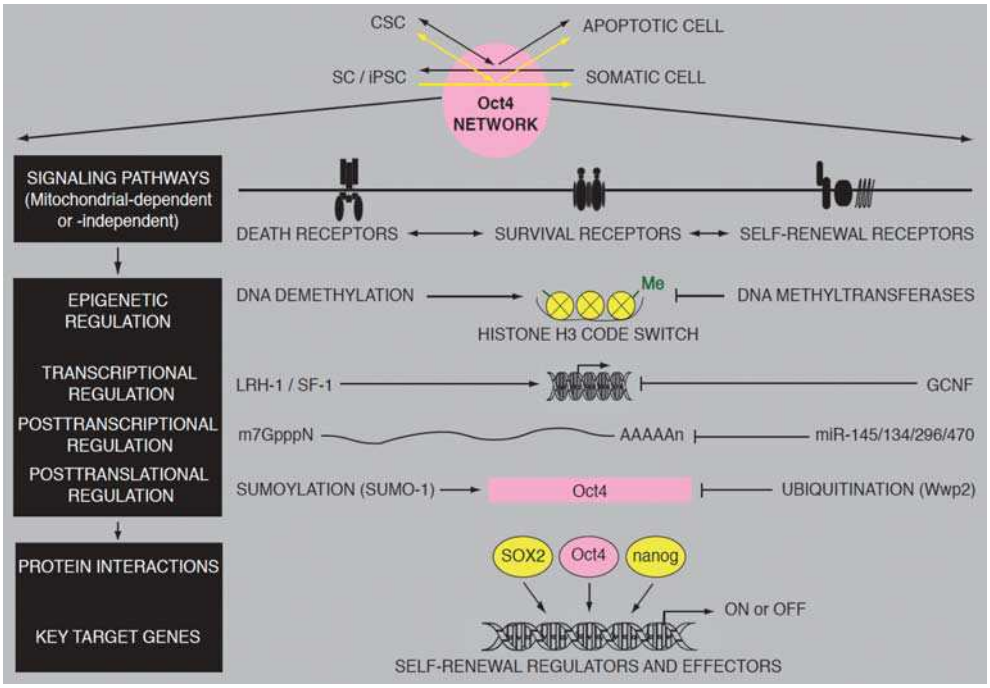

Fig. 5. Oct4 network. Several nodes of the Oct4 pathway, active in stem cells (SC), induced pluripotent stem cells (iPSC) or cancer stem cells (CSC), are potential targets for plant-derived compounds. Details relationships between the different actors can be found in section 2.4 of this chapter and in previous reviews [Kang et al., 2009; Shi & Jin, 2010]. Methylation of Oct4 promoter and specific modifications in the histone H3 code leads to a transcriptional repression of *Oct4*

Since the pioneering work of Yamanaka's laboratory in 2006, an exploding number of studies have unequivocally shown that ectopic expression of at least two transcription factors, namely Oct4 and SOX2, can reset the epigenome of somatic cells with restricted lineage-specific competencies to an highly undifferentiated pluripotent state [Feng et al., 2009; Takahashi & Yamanaka, 2006]. However the efficiency of the reprogramming process still remains very low, albeit a lot of effort has been put to improve the methods. Interestingly, *TP53* inactivation seems to facilitate significantly the embryonic SC switch, suggesting that a p53-mediated proapoptotic DNA damage response limits iPS cell

production [Marion et al., 2009]. Recently, it has been observed that reprogrammed pluripotent cells show genomic aberrations [Pasi et al., 2011]; this could explain why they can form malignant tumors when injected in donor mice [Sarig et al., 2010]. Induced Oct4-expressing somatic cells seem therefore to adopt a SC or CSC phenotype or to undergo apoptosis in a stochastical manner; this firstly suggests that Oct4 is only one of the key decision-makers in stemness and carcinogenic behavior (see top of Fig. 5). Elucidation of the precise molecular mechanisms through which Oct4 maintains and reinitiates pluripotency is thereby necessary before planning cell therapy using iPS. An improved understanding of Oct4 biology will also provide a number of novel targets for the design of specific phytochemical therapy that aims to eradicate poorly differentiated CSCs. Different sets of proteins located either upstream or downstream from the Oct4 pathway have already been identified (Fig. 5); however the mechanisms of action of certain pharmacological agents, such RA, capable to target specifically Oct4-centered protein interactomes have still to be clearly established. For that purpose, the evaluation of a selective action of a specific plant-derived compound on Oct4 network in CSCs has also to be considered, in regard to its potential side effects on normal SCs.

4. Conclusions and future perspectives

Conclusions of experimental data suggesting a potential biological activity of a plant-derived compound on a specific cancer and CSC type should be carefully analyzed. In view of the present chapter, it seems that only phytochemicals which can selectively target the ROS-induced proapoptotic and/or differentiation processes, have some promising therapeutic values. The main reason for this assumption is that CSCs, as well as cancer cells, share a nearly satured adaptability of the redox capacity and escape from the signals emitted by the well embedded and protective niche. In regard to their susceptibility to prooxidant stresses and, to a certain extent, to prodifferentiation inducers, it is expected that only CSC and their descendants could be selectively targeted by natural or synthetic plant-derived compounds. One of the best example is retinoic acid which is known to be the most powerful anticancer agent and is used with success in chemotherapy. However dosing schedules of a considered phytochemical is a critical point which has to be taken in account in order to minimize and, if possible, to avoid toxic side effects on normal cells and their progenitors.

Promising anticancer strategies have recently be developed by targeting CSCs. Although this chapter supports the anticancer benefits of phytochemical compounds, only future studies, likely using comparative well-defined CSC lines, will determine if they can reasonably act as selective chemopreventive agents in the key steps of the carcinogenic process. In this point of view, understanding the role of Oct4 in cancer stem cell biology is crucial for two main reasons. As an initial protein in the cancer cell hierarchy, and therefore as a reliable marker of cancer aggressiveness, its detection, as well as the available tools to repress its function, have strong prognostic and diagnostic values. Secondarily, as a key protein for somatic cell reprogramming, its controlled activity is a prerequisite for save immunocompetent cell regenerative therapy, without any harmful tumorigenic drift.

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Cancer Stem Cells - The Cutting Edge

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Over the last thirty years, the foremost inspiration for research on metastasis, cancer recurrence, and increased resistance to chemo- and radiotherapy has been the notion of cancer stem cells.The twenty-eight chapters assembled in Cancer Stem Cells - The Cutting Edge summarize the work of cancer researchers and oncologists at leading universities and hospitals around the world on every aspect of cancer stem cells, from theory and models to specific applications (glioma), from laboratory research on signal pathways to clinical trials of bio-therapies using a host of devices, from solutions to laboratory problems to speculation on cancersâ€™ stem cellsâ€™ evolution. Cancer stem cells may or may not be a subset of slowly dividing cancer cells that both disseminate cancers and defy oncotoxic drugs and radiation directed at rapidly dividing bulk cancer cells, but research on cancer stem cells has paid dividends for cancer prevention, detection, targeted treatment, and improved prognosis.

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