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Drugs that Kill Cancer Stem-like Cells

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1. Introduction

The hallmarks of cancer include processes like self-sufficiency for growth signals, insensitivity to growth-inhibitory (anti-growth) signals, evasion of programmed cell death (apoptosis), unlimited replicative potential, sustained angiogenesis, and tissue invasion and metastasis (Hanahan & Weinberg, 2000). Recent research dictates that these definitions, while valid, ought to be enriched. That is, we should also consider tumours as a heterogeneous ‘collection of cancer cells’ with a hierarchy. This ‘hierarchical hypothesis’ tells us that tumours contain a minute (sometimes very small) sub-set of cells with distinct properties from the bulk of the tumour mass (D’Amour & Gage, 2002; Visvader & Lindeman, 2008; Visvader, 2009). These cells feature certain characteristics inherent to stem cells, including the capacity of self-renewal, asymmetric division and differentiation. They have also a very high propensity to form tumours. Therefore these cells are referred to as cancer stem cells (CSC) or cancer stem-like cells or, better, tumour-initiating cells (TICs). The terminology, while not too important, may be misleading though, since the term ‘cancer stem cells’ implies that we are dealing with true stem cells, which is not possible to reconcile with at this stage, perhaps even more so, since the origin of CSCs is not exactly known.

Recent evidence, rather circumstantial, indicates that CSCs may have developed during the stage of tumour immunoediting (Dunn et al., 2002, 2004a). According to this concept, the immune system is actively involved in tumour initiation as well as progression, and this became known as the principle of ‘three Es’, involving the phases of ‘elimination’, ‘equilibrium’ and ‘escape’ (Dunn et al., 2004b). The elimination phase of the process of immunoediting is responsible for the detection and elimination of cells that became malignant, usually due to the failure of their tumour suppressor mechanisms (Smyth et al., 2002). The selection of such CSCs is depicted schematically in Figure 1. Here, certain cells, possibly with slightly different properties than the bulk of the cell population, survive the pressure of the immune system, while most of the cells are eliminated by the cells of the immune system such as the cytotoxic T lymphocytes (CTLs) (Schreiber et al., 1983; Bancroft et al., 1991; Smyth et al., 2001; Takeda et al., 2001; Hayakawa et al., 2002). These cells then give rise to a tumour. Upon therapeutic intervention, many cells of the tumour are induced into
apoptosis and die, while some survive and give rise to ‘second-line’ tumours with acquired resistance to the ‘first-line’ treatment, vastly complicating further therapy and making the prognosis very grim (Neuzil et al., 2007; Visvader & Lindeman, 2008; Alison et al., 2010; McDermott & Wicha, 2010).

Fig. 1. Possible selection of CSCs during cancer cell immunoediting and their contribution to the resistance of tumours to therapy. During the process of malignant conversion, several cells that carry mutations escape the elimination phase of the process of immunoediting, which involves a variety of cells of the immune system, such as natural killer cells, natural killer T cells, cytotoxic T cells or macrophages. These ‘selected’ cells form a tumour with relatively low number of CSCs. Upon challenge of the tumour with anti-cancer drugs, majority of the cells are killed via apoptosis, while the CSCs survive. They then start differentiating and proliferating to give rise to ‘second-line’ tumours with higher resistance to therapy, making them very hard to eliminate. The percentage of CSCs in the ‘second-line’ tumours is similar to that in the primary tumour.

2. Identification of cancer stem-like cells

CSCs have been, thus far, identified in a great number of tumours. Thus, CSCs have been described in multiple myelomas (Park et al., 1971) and in leukemias (Lapidot et al., 1994; Bhatia et al., 1998), after which they were also discovered in the neoplastic diseases of the nervous system (Singh et al., 2003; Piccirillo et al., 2006), colon cancer (Ricci-Vitiani et al., 2007), prostate cancer (Collins et al., 2005), hepatocarcinomas (Yin et al., 2007), breast cancer (Al-Hajj et al., 2003), melanomas (Fang et al., 2005; Schatton et al., 2008) and osteosarcomas (Gibbs et al., 2005), and we have recently identified CSCs in the context of malignant mesotheliomas (Neuzil et al., unpublished data).
One of the most vexing problems in the study of CSCs is their identification. A number of markers of CSCs or the combination thereof, varying, more-or-less, from cancer type to cancer type, have been described. Of the ‘markers’ used to define CSCs, many are cell surface proteins that endow the sub-set of CSCs with specific properties, and some have been involved in functional differences of CSCs when compared to the fast-proliferating, more differentiated cancer cells. However, different markers or their combinations have been proposed to characterize CSCs even within the same type of tumour. For example, breast cancer CSCs have been typified by the genotype CD44+/CD24−/ALDH (Ginestier et al., 2007; Charafe-Jauffret et al., 2009). We found breast cancer CSCs also upregulating CD133, while the CD24 status varies (Neuzil et al., unpublished data). Similarly, ovarian carcinoma stem cells have been described as CD44+/CD117+ (Zhang et al., 2008) or CD133+ (Baba et al., 2009).

Probably the most frequently used markers of CSCs are the surface proteins CD24, CD44, CD47, CD133, the level of expression of aldehyde dehydrogenase (ALDH), and the presence of the so-called ‘side-population’. These markers have been used to characterize CSCs from a variety of tumour types, although the use of some of these markers has been challenged. This controversy has been proposed, for example, for the probably most frequently used CSC marker CD133, with Shmelkov et al. (2008) having reported that metastatic colon cancer cells exert comparable tumour-initiating capacity regardless of the CD133 status.

While the glycoprotein CD24 has been shown to be downregulated in CSCs of some types of breast cancer, CD44 appears to be consistently upregulated in breast cancer CSCs (Al-Hajj et al., 2003; Ginestier et al., 2007; Charafe-Jauffret et al., 2009) as well as CSCs of prostate (Collins et al., 2005), pancreatic (Patrawala et al., 2006; Li et al., 2007), ovarian (Zhang et al., 2008; Alvero et al., 2009), colorectal (Du et al., 2008) and liver cancer (Yang et al., 2008). CD44 has been earlier identified as a receptor for hyaluronic acid, whose engagement may result in the activation of TGFβ signalling, promoting the pro-survival, anti-apoptotic pathways (Shipitsin et al., 2007).

Over the last few years, CD133 has been utilized most frequently as a marker of CSCs (Corbeil et al., 2001; Miraglia et al., 2007; Neuzil et al., 2007; Tang et al., 2007). The types of tumours that are typified by CSCs that exert high level of CD133 include such diverse neoplasias as breast cancer, colon cancer, tumours of the nervous system, etc. It is rather surprising that not too much is known about the function of the protein. CD133, also known as prominin-1, was first discovered in hematopoietic stem cells (Corbeil et al., 2001; Miraglia et al., 2007). It was shown that CD133+ cells have the propensity to form tumours in NOD/SCID mice even when low numbers of such cells were xenografted (Ricci-Vitiani et al., 2007; Yin et al., 2007; O’Brian et al., 2007; Wright et al., 2008). Even though Shmelkov et al. (2008) reported that in their hands, CD133- cells are also capable of tumour initiation in immunocompromised mice, they showed that CD133+ colon cancer cells exert much greater metastatic potential than their CD133- counterparts. Thus, regardless the reports doubting the usefulness of CD133 as a stem cell marker, prominin-1 can be used as a marker for the increase in the ‘stemness’ of the cell subpopulation, in particular in combination with other markers, such as CD44 and CD24.

A considerable problem in studying CSCs is, besides their identification, their maintenance in culture. For example, we studied CD133+ Jurkat cells from ‘mixed’ pre-separation population of the cells following their separation by immunomagnetic sorting, and found that the CD133high sub-population (over 60% CD133 positivity) reverted to the ‘mixed’ population phenotype with some 20% CD133-positive cells within several days after placing
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3. Compounds that kill cancer stem-like cells

Numerous studies have documented resistance of CSCs to established therapeutic modalities, including radiation therapy as well as chemotherapy. The reasons are multiple and include altered expression of genes that are important for initiation, progression and execution of apoptosis, activation of the survival pathways, and upregulation of transmembrane proteins that promote survival as well as activation of the DNA repair machinery. Increased resistance has been shown for many types of CSCs, including leukemic (Essers & Trumpp, 2010), brain (Bao et al., 2006; Liu et al., 2006; Hambardzumyan et al., 2006; Dirks 2010), pancreatic (Lonardo et al., 2010), breast (McDermott & Wicha, 2010), melanoma (Frank et al., 2003, 2005) as well as colon CSCs (Boman & Huang, 2008). Liu et al. (2006) found that CD133+ glioblastoma cells isolated from primary tumours were highly enriched in the products of genes that provide cells with survival advantage, which includes the anti-apoptotic genes Bcl-2, Bcl-xL, four members of the IAP family (c-IAP2, XIAP, NIAP and survivin) and, most notably the protein FLIP, while the expression of the apoptosis-promoting Bax was decreased. The caspase-8 inhibitor FLIP was upregulated up to 300-fold, pointing to its importance. The pattern of genes over-expressed in the CSCs suggests that the cells are well protected from induction and execution of both the intrinsic apoptosis mechanism (Bcl-2, Bcl-xL) as well as against the extrinsic pathway (FLIP). Moreover, the IAP family proteins inhibit the possible activation of multiple caspases. We found that CD133high cells, both Jurkat and MCF7, featured high level of expression of FLIP. This conferred their resistance to the immunological inducer of apoptosis TRAIL, which could be overcome by knocking down the FLIP protein using siRNA (Zobalova et al., 2008). Several types of CSCs have been reported to upregulate ABC pumps that make them
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Resistant to various chemotherapeutics. For example, ABCG5 has been shown to be upregulated in melanoma CSCs (Frank et al., 2003, 2005). Cells with high level of expression of members of the ABC pumps are classified as the so-called ‘side-population’, and these cells have been shown to possess a high re-populating activity when injected into NOD/SCID mice (Bhatia et al., 1998).

Finding efficient modalities to kill CSCs is undoubtedly of paramount importance and is a focus of intensive research. Thus far, the results are not particularly encouraging, although several potentially promising agents have been described (Table I). The first and probably best characterized is the sesquiterpene lactone parthenolide, a natural product isolated from medicinal plants including Tanacetum parthenium (feverfew) that has been initially found to inhibit the transcription factor NFkB (Bork et al., 1997), by way of inhibiting activation of the inhibitory components of the transcription factor (Hehner et al., 1998). However, it has been suggested that induction of apoptosis by parthenolide may be independent of inhibition of NFkB activation (Anderson & Bejcek, 2008). Since parthenolide proved efficient in suppressing the proliferation and inducing apoptosis of leukemia stem cells (Guzman et al., 2005a,b, 2007), a number of sesquiterpene lactones have been synthesized and tested as anti-cancer drugs (Ghantous et al., 2010). Parthenolide as a compound efficient in killing leukemia stem cells was confirmed using high-throughput, in silico screening (Hassane et al., 2008). The drug is now in Phase I clinical trial for several types of leukemia (http://www.globenewswire.com/newsroom/news.html?id=158480). Recently, breast CSCs as well as prostate CSCs have been reported as targets for parthenolide (Liu et al., 2008; Zhou et al., 2008; Kawasaki et al., 2009).

The mechanism(s) by which parthenolide kills CSCs is still obscure. Guzman et al. (2005b, 2007) reported that an analogue of parthenolide, dimethylamino-parthenolide, was very efficient in killing primary leukemic stem cells, which was replicated in pre-clinical models. It was found that induction of apoptosis in leukemia CSCs included generation of reactive oxygen species (ROS), inhibition of NFkB activation and activation of p53. An effect on NFkB was also proposed for inhibition of breast cancer CSCs by parthenolide as well as by other known inducers of the transcription factor, including pyrrolidinedithiocarbamate, using the mammosphere model of CSCs (Zhou et al., 2008). In prostate CSCs, parthenolide has been shown to exert also other activities than inhibition of NFkB or generation of ROS, which include inhibition of a variety of non-receptor and receptor tyrosine kinases as well as a number of transcription factors, such as C/EBPα, FRA-1, HOXA-4, c-Myb, Snail, SP1, etc. (Kawasaki et al., 2009). Of considerable clinical interest is combination of parthenolide with established anti-cancer agents. To this effect, Liu et al. (2008) reported that the combination of long-circulating (stealth) liposomes carrying parthenolide with those containing vinorelbine fully inhibited xenografts derived in immunocompromised mice from MCF7 cells. In cultured MCF7 cells sorted for the ‘side-population’ with high tumour-initiating potential, the combination of the two drugs exerted a very good anti-proliferative effect.

High-throughput in silico screening has been used recently in a search for compounds that would efficiently kill breast CSCs. This resulted in discovery of the well known agent salinomycin as an anti-CSC drug (Gupta et al., 2009), with a potential clinical application (Rowan, 2009). This agent was some 100-fold more efficient in lowering the proportion of CSCs in the cancer cell population than the established anti-cancer agent paclitaxel. Analysis of breast tumour xenografts in mice treated with salinomycin revealed that the agent promoted differentiation of the tumour cells and down-regulation of the breast CSC marker.
<table>
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<td>MitoVES</td>
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Table I. Small molecules killing cancer stem-like cells.

genes. A follow-up publication documented that salinomycin induces apoptosis in resistant cells, such as those expressing high levels of Bcl-2 and p-glycoprotein (Fuchs et al., 2009). Similar findings were also reported by Riccioni et al. (2010). Multidrug resistance, mediated by the ABC transporter proteins, was overcome by salinomycin in leukemic stem-like cells, inducing the resilient cells into apoptosis (Fuchs et al., 2010). Salinomycin, a potassium ionophore, is a product of the bacterium Streptomyces albus (Miyazaki et al., 1974), and has been used for a long time in poultry industry. A potential problem with the clinical application of the agent is its relatively high toxicity (Li et al., 2010) that may jeopardize its use in human medicine, quelling somewhat the enthusiasm for the future use of the agent.
Metformin is an oral anti-diabetic drug from the biguanide class, which has been used clinically as an efficient first-line agent against type 2 diabetes (Crandall et al., 2008). Recently this drug was reported to target breast CSCs and, when combined with doxorubicin, prevent growth of tumours as well as their remission (Hirsch et al., 2009). Another study documented that metformin could efficiently inhibit proliferation of breast CSCs refractory to the HER2-targeting agent Herceptin (trastuzumab) as well as their self renewal (Vazquez-Martin et al., 2010a). Since metformin acts by interfering with the energy metabolism of cells, it may inhibit self-maintenance of mitotically competent cells acting as a caloric restriction mimic (Martin-Castillo et al., 2010; Vazquez-Martin et al., 2010b; Nguyen et al., 2010).

A considerable problem in cancer management is encountered in the case of HER2-high breast cancer (Slamon et al., 1989). To this effect, the agent lapatinib has been applied as a drug of choice for Herceptin-resistant, metastatic breast cancer cells (Burris et al., 2005). This dual receptor tyrosine kinase inhibitor (suppressing the activation of HER2/erbB2 and EGFR) has been suggested to suppress the growth of CSCs in the context of HER2-high breast and lung tumours (Magnifico et al., 2009; Korkaya and Wicha, 2009; Diaz et al., 2010).

Several of the above agents reported to suppress tumour growth and, in some cases, prolong the remission-free period in experimental animals, act by inducing generation of ROS. In this context, we have been studying a class of anti-cancer drugs from the group of vitamin E analogues, epitomized by the redox-silent α-tocopheryl succinate (α-TOS) (Figure 2B) (Neuzil et al., 2001; Weber et al., 2002). This agent acts by targeting the mitochondrial complex II (CII), whereby causing generation of high levels of ROS, which then induce apoptosis by destabilizing the mitochondrial outer membrane (Dong et al., 2008, 2009), by promoting the formation of the Bak channel in mitochondria (Prochazka et al., 2010; Valis et al., in press). To enhance the activity of the vitamin E analogue, we modified the agent by its tagging with the positively charged triphenylphosphonium (TPP+) group, as suggested for a variety of redox-active compounds (Smith & Murphy, 2005; Biassutto et al., 2010), generating mitochondrially targeted vitamin E succinate (MitoVES) (Figure 2B). As indicated in Figure 2A, such TPP+-modified compounds move across most biological membranes. Upon crossing the mitochondrial inner membrane (MIM) with the negative potential on the matrix face, the agent is trapped and gradually accumulates in this compartment so that its local concentration is considerably increased. In the case of MitoVES, with its target CII within the MIM, such approach can be expected to maximize its biological activity. Indeed, we found that MitoVES was 1-2 log more efficient in killing cancer cells than the untargeted counterpart (α-TOS), which was paralleled by an effect on experimental cancer, including colon cancer and HER2-high breast cancer (Dong et al., 2011). We have recently found that MitoVES is very efficient in apoptosis induction in a breast cancer CSC model represented by mammospheres, which feature cells with enhanced level of stemness and which can be characterized as CD44high/CD133high/CD24low/Jagged-1high (Figure 3A,B). In fact, MitoVES was more efficient in killing the mammosphere cells than did the untargeted α-TOS and than parthenolide, probably thus far the best characterized agent toxic to CSCs (Figure 3C) (Neuzil et al., unpublished data). While the mechanism is not clear at this stage and much more work needs to be done, agents like MitoVES may present a substantial promise for the development of compounds that will efficiently eradicate not only the bulk of the tumour cells but, more importantly, also the highly recalcitrant CSCs, whereby minimizing the probability of tumour remission.
Fig. 2. **Principle of mitochondrial targeting.** A. Addition of a cationic, triphenylphosphonium (TPP⁺) group to hydrophobic compounds, with the charge on the phosphorus delocalised on the flanking phenyl groups, causes their relatively free movement across biological membranes. Once in the mitochondrial matrix with the negative potential on the matrix face of the mitochondrial inner membrane (MIM), the TPP⁺ group anchors the compound at the matrix-MIM interface, with increased concentration of the agent in this compartment. This is important for enhancing the bioactivity of agents, whose target is in the proximity of the interface. B. The structures are shown of the untargeted α-tocopheryl succinate (α-TOS) and the mitochondrially targeted vitamin E succinate (MitoVES).
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Fig. 3. MitoVES is efficient in killing mammosphere cells. A. The breast cancer cells (line MCF7) were cultured as adherent cells (MCF7) or as mammospheres (MS). B. Flow cytometric analysis characterized the adherent MCF7 cells as CD24\textsuperscript{high}/CD44\textsuperscript{low}/CD133\textsuperscript{low}, while the MS cells were CD24\textsuperscript{low}/CD44\textsuperscript{high}/CD133\textsuperscript{high}. We also found MCF7 cells low in expression of the stemness marker Jagged-1, which was increased in the MS cultures. Both CD133 isotypes were analysed here. C. The adherent MCF7 cells (top panel) and their mammosphere counterparts (lower panel) were exposed to 50 \( \mu \)M \( \alpha \)-tocopheryl succinate (TOS), 10 \( \mu \)M parthenolide (PTL) or 5 \( \mu \)M mitochondrially targeted vitamin E succinate, MitoVES (MVES), for the time periods indicated and the cells analysed for apoptosis level.

4. Conclusions

Cancer is now number one reason for the demise of human patients, having surpassed the number of deaths linked to cardiovascular diseases (Twombly, 2005), and the trend appears rather grim (Jemal et al., 2010). A factor contributing to this negative outlook is undoubtedly the hierarchical structure of tumours with a subset of cells with tumour-initiating properties. These cells share some features with stem cells, while they are tumour cells in that they are malignant. Experiments, in which CSCs were isolated from xenografts and used to give rise to a tumour in a serial manner, documented that, although more-or-less pure CSCs were used to initiate the tumour, the percentage of cells with stem-like properties were kept very similar in each subsequent experimental animal. This suggests that tumours are endowed with a level of plasticity and ‘memory’, which dictates that cells are always present in the tumour whose role is to make sure that the total population of cancer cells will not be eradicated. This ‘memory’, however, also includes additional mutations such that the ‘second-line’ tumours, derived from the CSCs that survived the therapeutic intervention, is resistant to the ‘first-line’ treatment, which considerably jeopardizes any therapeutic modalities applicable to such patients.

While every tumour has different properties, cancer cells also share many features. This may well be true also for CSCs from different types of tumours. Finding such common traits may help discover the Achilles’ heel of CSCs and, subsequently, devise efficient therapeutic
Fig. 4. Microarray data characterise mammospheres as a phenotype with increased stemness. A. Principle components analysis (PCA) of adherent (ADH) and mammosphere (SPH) MCF7 cell cultures shows that each phenotype clusters together. PCA projections are represented in 2D (left) and 3D (right) manner. B. Gene set enrichment analysis (GSEA) plots show enrichment of (i) embryonic stem cell (ESC) \( p = 0.044, \text{FDR} = 0.046 \), (ii) neuronal stem cell (NSC) \( p = 0.001, \text{FDR} = 0.006 \) and (iii) hematopoietic stem cell (HSC) \( p = 0.075, \text{FDR} = 0.085 \) gene sets in mammosphere but not adherent cultures. Each vertical line on the enrichment plot represents a probe in the corresponding gene set. The left to right position of vertical lines indicates the relative position genes from ESC, NSC and HSC gene sets within the rank-ordered list of the 37,805 probes present on the HumanHT-12 BeadChip. The first probe on the left represents the most upregulated probe in adherent samples and the last on the right represents the most upregulated probe in the sphere-forming samples. Probes in the middle are not differentially expressed.
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approaches. There are studies that attempted to characterize the global difference of gene expression in fast-proliferating tumour cells and the corresponding CSCs, and such studies have been useful for confirming the stemness features of the cells (Ivanova et al., 2002; Ramalho-Santoz et al., 2002; Fortunel et al., 2003) or to characterize specific properties of CSCs (Birnie et al., 2008).

We have attempted to use microarray analysis to characterize the stemness of several types of cancer cells grown as spheres, including breast and prostate cancer as well as malignant mesotheliomas (Figure 4) (Neuzil et al., unpublished data). Using this approach, we identified increased stemness in all three types of cancer. Moreover, the tools of bioinformatics allow us to search for features that are shared by the different types of model CSC cultures. We found that the three types of CSCs share certain pathways, including glycolysis and oxidative phosphorylation, which suggests that the use of agents like MitoVES (c.f. Figure 3) may be a way how to kill such cells. Further and probably most intriguingly, we found that of all the shared pathways that are upregulated in the three types of CSCs, tryptophan metabolism (represented by increased expression of IDO) is the most activated pathway. This is a highly interesting result, which suggests that CSCs are endowed with activity that results in lowering the level of tryptophan in their ‘neighborhood’. Depletion of tryptophan (especially due to upregulation of IDO) is one way how cancer cells may protect themselves from the immune surveillance, providing the cancer cells with both passive and active defense mechanisms (Munn & Melor, 2008; Löb et al., 2009), and inhibitors of IDO, such as brassinin or 1-methyl tryptophan, are being considered as anti-cancer drugs (Gaspari et al., 2006; Hou et al., 2007).

It is therefore very tempting to speculate that a highly efficient way to eradicate tumour cells, including the fast-proliferating ones and the resistant CSCs, may be the combination of agents like MitoVES that would kill the bulk of the tumour cells, while the IDO inhibitor would allow for the cells of the immune system to attack the remaining tumour cells, likely those with higher level of ‘stemness’. Although a lot of work remains to be done, we propose that such a strategy may be potentially developed and applied in the clinic to minimize the probability of cancer relapse.

5. References


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Cancer Stem Cells Theories and Practice does not 'boldly go where no one has gone before!' Rather, Cancer Stem Cells Theories and Practice boldly goes where the cutting edge of research theory meets the concrete challenges of clinical practice. Cancer Stem Cells Theories and Practice is firmly grounded in the latest results on cancer stem cells (CSCs) from world-class cancer research laboratories, but its twenty-two chapters also tease apart cancer's vulnerabilities and identify opportunities for early detection, targeted therapy, and reducing remission and resistance.

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