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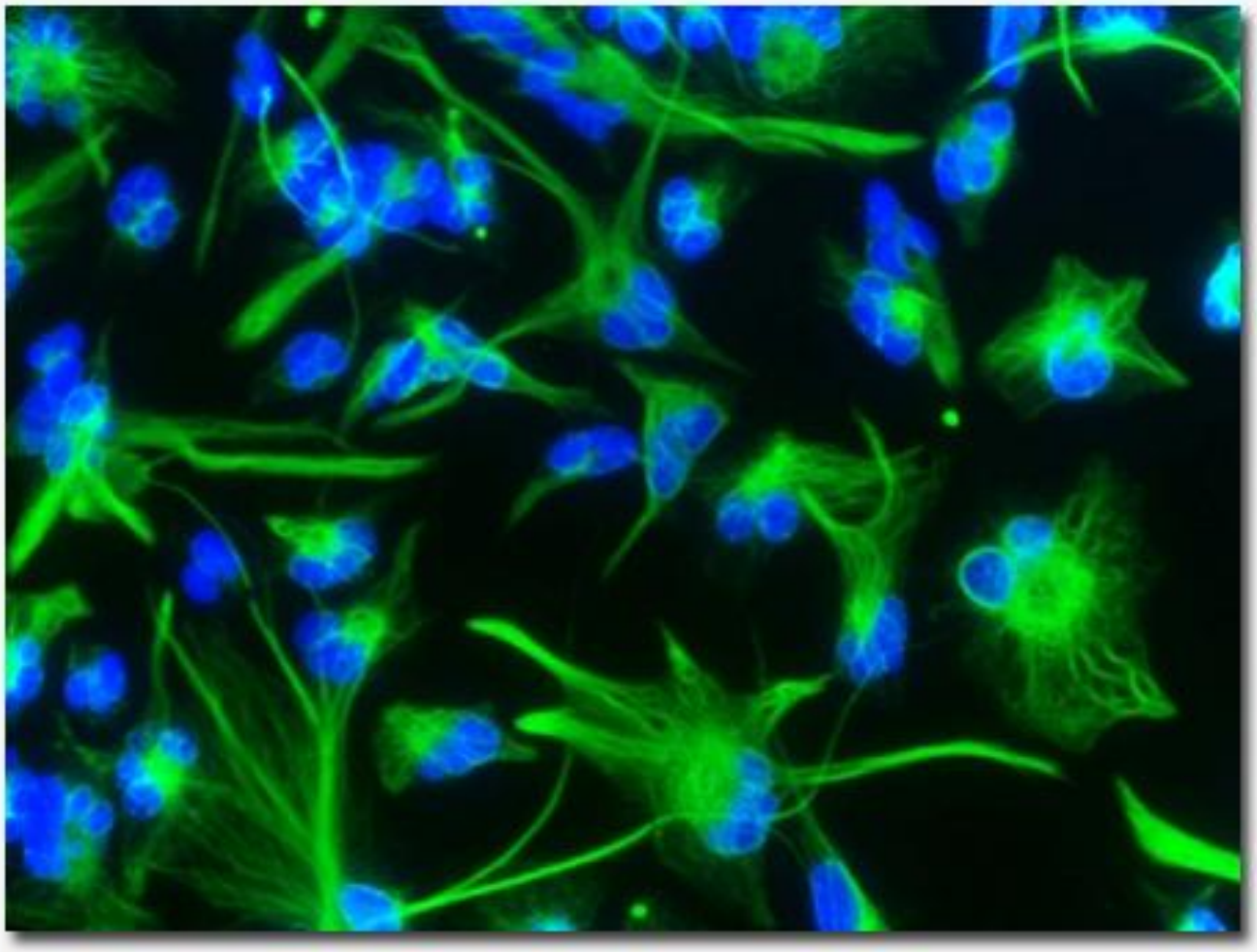
The DNA damage response in cancer stem cells



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Abbreviations

DNA: Deoxyribonucleic Acid

DSBs: Double strand breaks

CSCs: Cancer stem cells

DDR: DNA damage response

NHEJ: Non homologous end joining

HR: Homologous recombination

ATM: Ataxia Telangiectasia Mutated kinase

ATR: ATM and Rad3 Related kinase

Nbs1: Nijmegen Breakage Syndrome 1

Chk1 & 2: Checkpoint protein 1 & 2

Cdc25: Checkpoint dependent cyclin 25

PML: Promyelocytic leukemia protein

IR: Ionizing Radiation

BRCA1: Breast cancer gene 1

CSCM: Cancer stem cell model

BER: Base excision repair

NER: Nucleotide excision repair

Hh: Hedgehog gene

GSCs: Glioma stem cells

PI3-K: Phosphatidylinositol-3-kinase

HSCs: Hematopoietic stem cells

Abstract

In present day cancer therapy, patients are often treated with DNA damaging agents to induce excessive DNA damage in cancer cells in addition to other treatments such as surgery. The aim of these treatments is to induce apoptosis in cancer cells, nonetheless not all cancer cells die from such treatments.
In recent years it has been described that there are subpopulations within tumor cell populations. In the cancer stem cell model, the structure of these subpopulations is described. It is assumed that so called cancer stem cells, or tumor-initiating cells form the foundations of tumors. In this model it is also described that cancer stem cells are the driving force of tumor growth and are highly resistant for therapy. Cancer stem cells were suggested to have a different response to DNA damage when compared to non-tumor-initiating cancer cells. This implicates that they need a different treatment than other cancer cells, before they acquire such an amount of DNA damage that they go into apoptosis. Not only inducing DNA damage is a way to eradicate cancer stem cells. Other ways of doing so for example is to destroy the niche the cancer stem cells need to keep their stem-like capacities, or sensitize them to DNA damaging agents. When these cells are not treated differently it is possible that they repair the damage that treatment has caused and may continue to divide and proliferate.
It is important to know how these cancer stem cells react to DNA damage, because there is evidence that in a vast majority of tumors both solid and humoral, cancer stem cells are present. It is not yet known how exactly the DNA damage pathway of these cells differs from that of non-tumorigenic stem cells and other cancer cells.

Introduction

The size of different organs in the body is dependent on three factors; cell growth, cell division and cell death.[1] All these three things have to be in balance to keep organs and thereby the body healthy. In tumors this balance is missing. The cell division rate is higher than the cell growth and rate of cell death. In order to stop the tumor growth the rate of cell death has to be increased or the division rate decreased.

Modern day medicine focuses on both sides of the balance scales by treating almost all cancer patients with radiotherapy or chemotherapeutic agents. With these treatments the DNA of the cells is damaged to such an extent that cells are forced to activate the process of apoptosis. In this way they both increase the cell death rate and decrease the division rate. But even if the treatment seems successful a number of tumors relapse. In these cases, even if the tumor appears to almost be vanished, ultimately tumor cells start growing again. This indicates that not all tumor cells are destroyed by the treatment with radiotherapy or chemotherapeutics.

Somatic stem cells divide very slowly and give rise to progenitor cells which in turn give rise to the tissue cells that we know. The stem cells itself are mostly dormant and they are able to renew themselves. In the cancer stem cell model it is assumed that the cells that remain after treatment often are able to renew themselves, have differentiation capacities and continuously sustain tumor growth. These cells are mostly dormant and divide very slowly.[2] These cells too are pluripotent, meaning that they can form any kind of cell of the same tissue. Because of their pluripotency and self-renewal capacities they can proliferate rapidly into a new full grown tumor.
These capacities are thus almost the same as in somatic stem cells that can be found in almost all types of tissue in the body. Since these cells have much the same characteristics as non-tumorigenic stem cells they are called cancer stem cells (CSCs) or tumor-initiating cells. Still, this model is young and not free from controversy, and multiple names are used to indicate tumor cells with stem-cell like properties, such as cancer stem cells, tumor-initiating cells or neuronal progenitor cells. For this thesis I will call them cancer stem cells or CSCs, but other names can be used instead.

There is evidence that CSCs respond worse to radiotherapy and chemotherapy because they have an altered DNA damage response (DDR)[3] compared with cancer cells without stem-like properties. This can be the reason that they are so difficult to destroy with current therapy. In order to treat patients properly and make sure that all the cancer cells die after treatment one has to be sure that the CSCs also vanish. This might imply that these CSCs have to be treated differently than the other cancer cells, and that patients have to be treated with different kinds of treatment next to the normal treatment to get the desired result. But the one ‘magic bullet’ to get rid of the CSCs is to this day unknown.

In this thesis I shall explore how the DNA damage response in CSCs differs from that of other cancer cells. Furthermore I shall focus on the ability of CSCs to repair damaged DNA inflicted by DNA damaging agents. Also alternative ways of eradicating CSCs shall be discussed.

The DNA damage response in cancer cells

Human cells have during the cell cycle several checkpoints of which three are DNA damage checkpoints (arrows, Figure 1). The first DNA damage checkpoint is at the G1-S-phase border, the second during inter-S-phase and the third during the G2-M-phase border. These checkpoints are essential for the integrity of the DNA. If DNA damage is detected at one of these checkpoints, the cell cycle is stalled and the damage is repaired by various pathways. In different stages of the cell cycle different repair mechanisms are used.

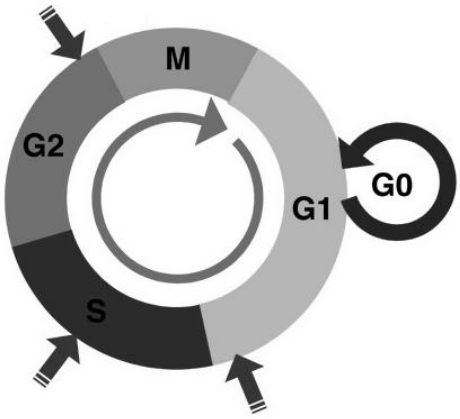
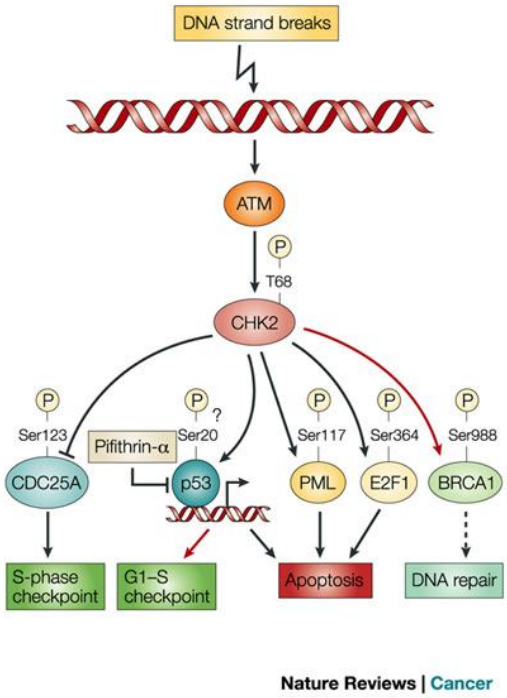


Figure 1. Cell cycle with DNA damage checkpoints. (www.iam2be.net)

As mentioned before, present day cancer therapy is based on surgery, often in combination with chemotherapy and radiotherapy. Both of these treatments inflict, amongst other types of damage, single or double strand breaks in DNA. Of all types of DNA damage, double strand breaks are probably the most dangerous to the integrity of the DNA and most cytotoxic. Cells use in the different stages of the cell cycle different repair mechanisms to repair this kind of DNA damage. In G0 or G1-phase the DSBs are mainly repaired by non-homologous end joining (NHEJ). During the rest of the cell cycle homologous recombination (HR)[4] is used. Ataxia Telangiectasia Mutated kinase (ATM) has a role in both repair mechanisms.

DNA damage repair pathways

ATM is a major player in the pathway that senses and repairs double strand breaks.[5,6] When damage is inflicted in a dividing cell the damage has to be repaired before the cell goes further into the cell cycle. The cell cycle is stalled when damaged DNA is detected. At the sites of DSBs several proteins are assembled such as ATM and ATR (ATM and Rad3 related kinase) kinases. Both however are recruited in a different way. ATM is recruited to the DSB site by the Mre11–Rad50–Nbs1 (MRN) complex, and ATR is recruited to sites with stalled replication forks by the ATR-interacting protein or after UV-radiation.[7] This recruitment of ATR only happens in S and G2-phase after IR. ATM recruitment is always present. Results of Jazayeri *et al.* show that both ATM and ATR are necessary for the phosphorylation of Chk1 after treatment with IR and IR-mimetic drugs[9]. ATM together with Nbs1 phosphorylates proteins such as Chk1 and Chk2. The activation of Chk1 and Chk2 by ATM happens after Ionizing Radiation (IR) (Figure 2).



Chk1 and Chk2 in turn activate DNA damage checkpoints by phosphorylating downstream proteins such as Cdc25 and p53 which can cause cell cycle delay and apoptosis.[8] As one can see in Figure 2 there are several outcomes to the activation of ATM. The cell always stalls the cell cycle via Cdc25 and p53, but it can also go into apoptosis via p53, PML and E2f1. DNA repair itself is done via NHEJ or homologous recombination, which is initiated via the MRN-complex.[9] BRCA1 is also believed to have an influence on this pathway but its precise role is still unknown.[11,5] PML is a

tumor suppressor gene that regulates the p53 response to DNA damage during the cell cycle.[10] E2f1 is known to activate p53 dependent and independent apoptosis and can enable cell proliferation.[11]

Non-homologous end joining and homologous recombination

Non-homologous end joining is a procedure whereby the two broken strands are joined in a DNA sequence independent fashion.[4] Because of the break, base pairs on both sides of the nick may be destroyed.[1] With NHEJ these base pairs are not replaced. Since there is no template strand on which the repaired part of DNA is synthesized there is no control whether both parts of the DNA's double helix are exactly in the right place. So if the nick is exactly within a gene, small parts of DNA can be deleted and there is a high chance that the affected gene will not function properly anymore. NHEJ is one of the most common DNA repair mechanisms of double strand breaks and it can be used throughout the cell cycle.[1,6] It is probably because of the quick repair, that this repair mechanism is often used. Furthermore the fast majority of the DNA is not coding for genes, so if there is a mistake, the chance that genes are affected is very small.

Another DSB repair mechanism is homologous recombination. With this mechanism, homologous sequences to the damaged DNA are used as a template to repair the damaged part. Primarily, the damaged DNA is resected after which the single strand of DNA is used to invade the template DNA. This resection is initiated by cell cycle checkpoints that are ATM dependent and subsequently induce ATR signaling.[12] In S-phase and G2-phase the sister chromatid is used as a template to insure the genetic stability is secured.[13] If there is no homologous part of the DNA nearby, NHEJ is used to repair DSBs. [5] HR repairs DNA in a safe, controllable and highly efficient way.[6] Nevertheless, DNA repair does not only depend on these two mechanisms. There are other DNA damage repair pathways, such as the pathway described below.

Excision repair

The above described repair mechanisms are not the only ways to repair DNA. The cell has other pathways at its disposal such as base excision repair (BER) or nucleotide excision repair (NER) to repair DNA damage. Most of the damaged bases in the DNA are repaired by BER.[14] During BER the wrongful DNA base is excised and replaced with the correct base by consecutive actions of DNA glycosylase, DNA polymerase and DNA ligase. [15] The opposite base on the complementary strand is used as a template to complete the base pair. NER on the other hand is very efficient in repairing bulky lesions in the DNA and it is mostly used on DNA damage caused by UV-radiation from the sun.[16] During NER, the DNA-helix is opened up around the flaw in a region of about 24-30 nucleotides. Subsequently incisions are made around this region and the whole region is repaired and replaced.[16]

The cancer stem cell model

Now we know how DNA damage repair is organized in response to common DNA lesion caused by anti-cancer therapy, it is important to know how these mechanisms differ in cancer cells as opposed to CSCs. To understand the importance of the presence of CSCs one first has to know about the cancer stem cell model. As discussed in the introduction, there is evidence that there are cancer stem cells present in tumors of patients. There are several reasons why these specific cells are so important for cancer research, as I will discuss below.

The former cancer initiating model rests on the fact that when cells acquire enough mutations in their DNA (especially in the oncogenes or tumor suppressor genes) the cell can become tumorigenic, and give rise to a tumor. The cancer stem cell model rests on the fact that tumors arise from CSCs or cancer initiating cells that are present in the body. In the last several years there is more and more evidence that tumors indeed arise from these kinds of cells. With this evidence the idea that a tumor can arise from any cell in the human body might become disputed.[17]

Bonnet *et al.* have mentioned in 1997 that leukemic cells are arranged in a hierarchical order with different types of cells.[18] This finding can be the predecessor of the present-day cancer stem cell model (CSCM.)
The CSCM consists of several criteria to which a cell has to suffice before it can be named a cancer stem cell. The tumor stem cell model describes a hierarchical organized group of cells, which is responsible for the tumor initiation, self-renewal and maintenance. These cells are also believed to be responsible for radio therapy resistance and mutation accumulation.[19, 20] CSCs have to be at least multipotent, so they can give rise to all types of cells from one certain type of tissue. Another part of the cancer stem cell theory is that the cancer stem cells express certain markers on the surface of the cell such as CD133 or CD34. However, not all researchers agree on the fact that CSCs can be identified by their surface markers, since research on the surface markers is not all consistent with each other.[5,10]

Evidence for the Cancer Stem Cell Model
The first evidence for the CSCM was found when researchers showed that a small group of cells was capable of giving rise to new acute myeloid leukemia cells when most of the leukemic cells did not have this ability.[21] According to Bonnet *et al.* and O´Brien *et al.* there is evidence that leukemia cells and solid tumors have different types of proliferating cells that all have tumorigenic qualities. Yet, not all cells have the ability to differentiate and proliferate when they are fully grown. The division of CSCs is mostly asynchronous, this means that the dividing cells gives rise to one daughter cell with stem cell capacities and one cell with differentiation capacities. Furthermore, Cho *et al.* have found that in murine mammary tumors, cells expressing the markers $THY1^{+}/CD24^{+}$ had a highly enriched tumorigenic activity.[22] However, these cells represented only 1-4% of the total tumor mass. Nonetheless, these cells were capable of surviving and initiating tumor growth in series of passages, where the other 96% could not. The cells of the formed tumors could be divided in tumor initiating cells and non-tumor initiating cells. This indicates that there are indeed different types of cells inside a solid tumor, which originate from a single group of cells with stem-like capacities. It also indicates that CSCs have a different type of survival strategy than cancer cells have.
Cancer stem cells are not limited to only to breast cancer and leukemia, in increasingly more types of cancer CSCs are found

Somatic stem cells in the human body
Not all cells in our body divide continuously, in almost all types of tissue in the human body stem cells are present. For very basal things we depend on the existence of cells with stem-like capacities. Our red blood cells are replaced every two to three months by new red blood cells from the bone marrow which derive from

hematopoietic stem cells. Another example is of the bowel, where the cells of the intestine have very high proliferation rates, which all derive from stem cells. As one can see stem cells are omnipresent throughout our body. Their task is to replenish cells that are lost or damaged by natural causesand so preserve tissue homeostasis.

Proliferation inside the tumor

There is evidence that CSCs originate from somatic stem cells that have acquired several mutations. These adult stem cells are multipotent and need interaction and continuous contact with tumor stromal cells to keep their stem-like capacities.[23]
The sonic hedgehog (Hh) gene is necessary for tumor growth in mouse pancreatic xenographs.[24] Without the Hh signaling, the CSCs do not self-renew. This is also the case for several solid tumors in humans such as glioblastoma and breast cancer. Not only the sonic hedgehog genes are important for the self-renewal of the CSCs, also the Wnt pathway is essential for the proliferation and self-renewal of CSCs in a number of tumor types.[25, 26]

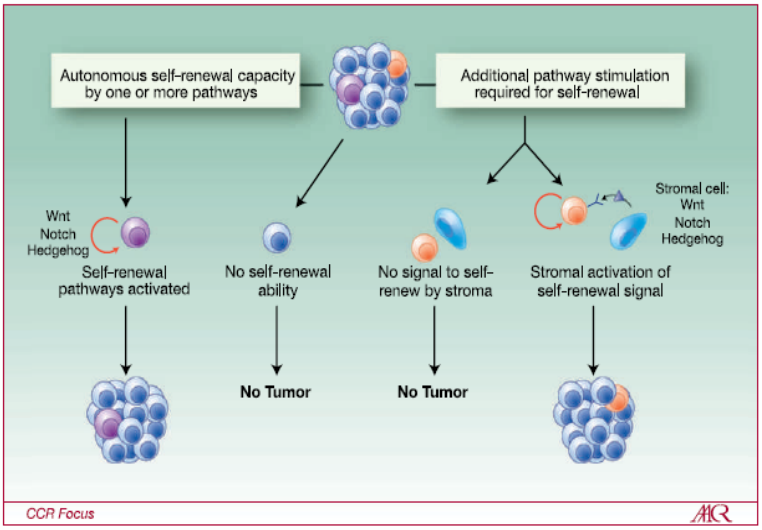


Figure 2. Schematic overview of self-renewal abilities of cancer stem cells with or without stromal cells. (O'Brien *et al.)* The stromal cells are essential to sufficient self-renewal systems for the cancer stem cells. Without signals from stromal cells there is no self-renewal. Only by stromal activation a tumor can grow, and sustain growth.

The stem cell model can be very convenient to treat all sorts of cancer in the same way. Cancer stem cells are found in many different types of cancer. There are CSCs isolated from common tumors, such as: breast cancer, tumors in the brain, colon, head & neck, pancreas, skin, liver, lung, prostate and ovaries. Also are CSCs found in myeloid leukemia.[14] If all these cancer stem cells have the same way of dealing with DNA damage it can be possible to treat these tumors in the same way. It would imply a massive decrease in costs of curing cancer in patients. Also if the cancer stem cell model is generally accepted and suitable for using in treatment of cancer patients, research could focus on the essence of these cells, to give eventually full recovery of the disease cancer. One part of understanding the cancer stem cell is to know how its DDR functions.

Possible targets in differences between cancer cells and cancer stem cells.

There is little but strong evidence that cancer stem cells have different ways of coping with DNA damage. This indicates that different treatments have to be created for the cancer cells and the CSCs. It is the CSCs that need to be under the focus of the future cancer therapy. Just as somatic stem cells, CSCs may divide very slowly and rarely. This can be one way why these cells accumulate less DNA damage. Because of the very rare division pattern, the cells have almost no duplication induced damage in their DNA so there is less DNA damage to be repaired than in other cancer cells which do divide frequently. Furthermore, some chemotherapeutics only targets some phases of the cell cycle, such as topoisomerases, which only affect cells in S-phase. Since CSCs primarily stay in G0 most of their life these kinds of chemotherapeutics will not affect them.

Tumor environment

As can be seen in Figure 3, without stromal signaling the CSC loses its self-renewal capacities. Just as differentiated cells in tissues, cancer cells without their proper niche can divide a limited amount of times before they go into apoptosis or senescence. The cancer stem cells however, do not have this limitation. Another

option is treatment with agents that affect the niche of the CSCs. The niche of the CSCs in solid tumors consists of stromal cells and when these are affected the tumor has no way of replenish the cells that have gone in apoptosis, and the tumor will hopefully disappear over time. Other possibilities to treat the CSCs are sensitization to IR or chemotherapy, or reduce the efficiency or activation of the DDR. Researchers try different ways to target specifically the CSCs but they do not always agree on the way how these cells have to be targeted. Cancer research is a field of research which is constantly in motion so there is good hope that the right target is found. In the next chapter I will discuss the ways in how the cancer stem cell DDR differs from the DDR in other cancer cells.

The DNA damage response in cancer stem cells

It has become known that CSCs react differently to the DNA damage inflicted by therapy than other cancer cells. It is not completely known in detail what these differences exact are. However, some things are known or can be extracted from the DDR in somatic stem cells.

In some ways the DNA damage response in CSCs is quite similar to that of other cancer cells. In research of Bao S *et al.* is found that glioma stem cells (GSCs) activate the same DNA damage pathway as the non-CSCs via ATM kinase. In this pathway ATM phosphorylates Chk1 and Chk2 and cause a cell cycle delay via p53. However, phosphorylation of the DNA damage checkpoint proteins such as Chk1 and Chk2 is much higher than in other cancer cells and thus the activation of the cell cycle checkpoints is higher.[5] This indicates that GSCs have a higher DNA damage checkpoint activation than normal cancer cells do. In this same article is also found that IR increases the activity of ATM in CSCs more than in other cancer cells and that the damage to the DNA is probably more efficiently repaired compared to other cancer cells.

Research of Zhang *et al.* has shown too that CSCs in mammary tumors in mice repair DNA damage more efficiently than other stem cells. This efficiency can be explained by the fact that an increased Akt signaling was found, indicating that apoptosis was inhibited, and thus cell survival was increased.[27]The Akt pathway is associated with radiotherapy resistance in human tumor cells and is closely related to PI3-kinases which are involved in tumor-cell proliferation.[28] This pathway is also activated in other cancer cells, so it is not entirely unique for CSCs. It was found in this same study that Akt may directly regulate the Wnt/β-catenin pathway by phosphorylating β-catenin on Ser552. In addition they found that β-catenin expression indeed increases and other Wnt target genes are activated such as survivin which is known to be over expressed in various types of tumors.[29] These last results were obtained from isolated CSCs indicating that the Wnt/β-catenin pathway is exclusively activated in the stem-like cells in a tumor cell population.

As mentioned in a previous chapter, E2f1 transcription factor has a role in cell proliferation and apoptotic pathways in a p53 dependent and independent fashion. E2f1 is also important because it has a pro-surviving role and prevents DNA damage in dividing cancer cells.[30] There are several forms of E2f, of which some are inhibiting apoptosis (E2f1) and others have an activating role in inducing apoptosis (E2f3).[31] In retinal progenitor cells both forms are present; however, it is not yet established what the functions of these transcription factors for the CSC imply. Since both forms have opposite functions inside the retinal progenitor cells it may be possible that CSCs have more E2f1 than E2f3 than other retinal cancer cells have. It can be that this transcription factor not only has a role in retinal blastoma, but also has a role in other types of cancer.

The tumor suppressor gene PLM is responsible for the cell fate in both stem cells as progenitor cells in blood, brain and breast tissues.[32] Loss of PML in hematopoietic stem cells (HSCs) in mice results in a higher amount of long-term repopulating stem cells than were found in HSCs positive for PML. Loss of PML in these cells also resulted in the re-entering of the cell cycle explaining the higher amount of new HSCs. This might result why PML deficient cells react worse on anti-cancer therapy than PML positive cells. When PML is lost not only a tumor suppressor is lost, but even worse, the tumor starts growing even faster. This gene is certainly a factor worth considering.

It has been shown by research of Karimi-Busheri *et al.* that breast cancer stem cells use a different DNA damage repair pathway than other cancer cells do. It has been shown by this study on MCF-7 cell cultures that these cells probably repair DSBs in a γ-H2AX independent fashion. Other cancer cells need the presence of γ-H2AX before the DSB can be repaired. γ-H2AX is necessary to recruit ATM and other DNA damage proteins to the site of

double strand breaks. It is striking that these MCF-7 cells do not need γ-H2AX to start the DNA damage repair pathway. However, researchers have not yet discovered how the recruitment of essential proteins is done.
What is known from this research is that breast cancer stem cells too have a quicker way of single strand break repair and base excision repair than other breast cancer cells[33].

Thus I can conclude from these articles that the DDR of CSCs do have some similarities with other cancer cells but use these pathways differently. Increased phosphorylation of several proteins such as Chk1 and Chk2, Wnt, and Akt help the CSC to repair the DNA damage quicker and more efficiently than the cancer cells without stem-like capacities. Greater activation of almost all described DNA damage proteins and increase expression of the discussed genes is probably the main reason that CSCs can repair DNA damage more easily than non-stem-like cells do. As is known so far, CSCs do not use very different pathways or different proteins to repair their DNA damage. So researchers have to focus on the DNA damage pathways and proteins of other cancer cells already known and trying to find a way to inhibit or over express these pathways and proteins to induce apoptosis not only in the CSCs, but also more excessive in other cancer cells. The CSCs from the different types of tumors do not differ much when it comes to their DDR so it is likely that when the pathways are unraveled in one type of CSC this information can be used for research in other types of CSCs.
It is still unknown what kinds of repair CSCs use; most research is focused on the expression of proteins or activation of certain pathways. More research has to be done to give any information about the way these cells repair DNA damage, either via NHEJ, HR, or maybe only via BER and NER.

Clinical implications

If one looks on the bright side CSCs can be a valuable factor for the treatment of cancer patients. If a specific target protein or receptor can be found to target the CSCs, complementary therapy can be given to each patient to decrease the risk of relapse. Also more specific research can be done on CSCs and so improve the anti-cancer therapies. If one looks on the dark side, the presence of CSCs is a disappointment. The fact that only ten cells with stem-like capacities are enough to replenish a tumor is at least depressing and chances of destroying all CSCs are very slim.[20] Nevertheless, more and more evidence starts to appear that the therapy resistance of those last ten cells can be disrupted too.

Sensitization of the cancer stem cells

Notch inhibition of cancer stem cells leads to decreased proliferation and self-renewal rates in Glioblastoma Multiforme brain tumors. Notch is part of a short pathway which is responsible for giving fate signals to the cell.[13] Fate signals determine if the cell has to migrate, grow, differentiate etc.[34]

The decreased proliferation of the CSCs can be an advantage because these cells then cannot produce new daughter cells. Moreover, the decreased proliferation and self-renewal rates give genotoxic agents more time to affect the DNA of the CSC. This might implicate that a smaller dose of DNA damaging agents can be administered to patients to obtain a similar effect.

Research of Bao *et al.* has shown that CSCs are sensitized to IR when the checkpoint kinases Chk1 and Chk2 are inhibited.[5] Since CSCs have an increased checkpoint activity, it makes sense to inhibit checkpoint kinases to induce more DSBs after treatment with IR. According to research of Song *et al.* Akt inhibition too sensitizes CSCs significantly to IR and inhibits the self-renewal of CSCs.[20] This can indicate that via the Akt pathway both sides of the balance are affected. Primarily more apoptosis is induced in the cells and secondly, CSCs lose their ability to replenish the damaged cells. These sensitizing tricks can be of great influence on the treatment of cancer. Since the DNA damage pathway is at some points the same as in normal cancer cells[3], one has to think of a way to tone down the efficiency of the DNA repair in CSCs. Inhibiting certain pathways such as Notch, Akt or the checkpoint kinases is one way to do that.

Removing temptations

Instead of sensitizing the CSCs or finding ways to inflict more DNA damage to cancer cells, one can also alter the niche the CSCs need to flourish. The CSCs need to have contact with stromal cells of the tumor to keep their stem like capacities.[16] When these stromal cells are destroyed, the CSCs loses its self-renewal capacity. This means that no more CSCs are produced and CSCs will be more sensitive to cancer therapy and it might decrease the risk of relapse after anti-cancer treatment.

Somatic stem cells and CSCs share numerous characteristics. This might implicate that the DDR of these groups of cells are also alike. So to trigger the DDR of CSCs it may be that the same mechanisms have to be triggered as in somatic stem cells. However, as mentioned before, this is not enough to get CSCs in apoptosis. The cells first have to be sensitized to the genotoxic agent and then treated with already known cancer therapeutics such as cisplatinum, paclitaxel or Bortezomib.

Furthermore cancer cells express telomerase, so that the telomere does not shorten after each division.[35] If this telomerase can be targeted, the telomere-tail of the DNA shortens after each division, and the cell dies after a couple of divisions, just as any other cell in our body.

I personally think that researchers are on the right track with the sensitization of the cancer stem cells via e.g. chk1 and chk 2 inhibition and targeting specific pathways that are needed in both cancer cells as well as cancer stem cells. I do not think that there is one ‘magic bullet’ to destroy the CSCs together with the normal cancer

cells. In my opinion treatment should consist of pre-treatment to sensitize the CSCs, complemented with normal radiotherapy or chemotherapy. Surgery to get rid of the tumor as a whole is still the best option I think, but sadly this is not always possible. The great challenge of the treatment of CSCs is to not destroy all the somatic stem cells, which the body still needs. I think that treatments with encapsulated chemotherapeutics or sensitizing agents will make the best effort to overcome this challenge. The somatic stem cells will not be or only slightly be affected by the treatment because the agents are released near to the tumor itself. Also experiments with immunological treatments directed against the specific CSC surface markers look promising.
Still researchers have a long way to go to cure the disease called cancer. Nonetheless, I think that one day it is possible to cure the surplus of all cancer types. But not with one type of treatment, but with several treatments combined with each other.

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