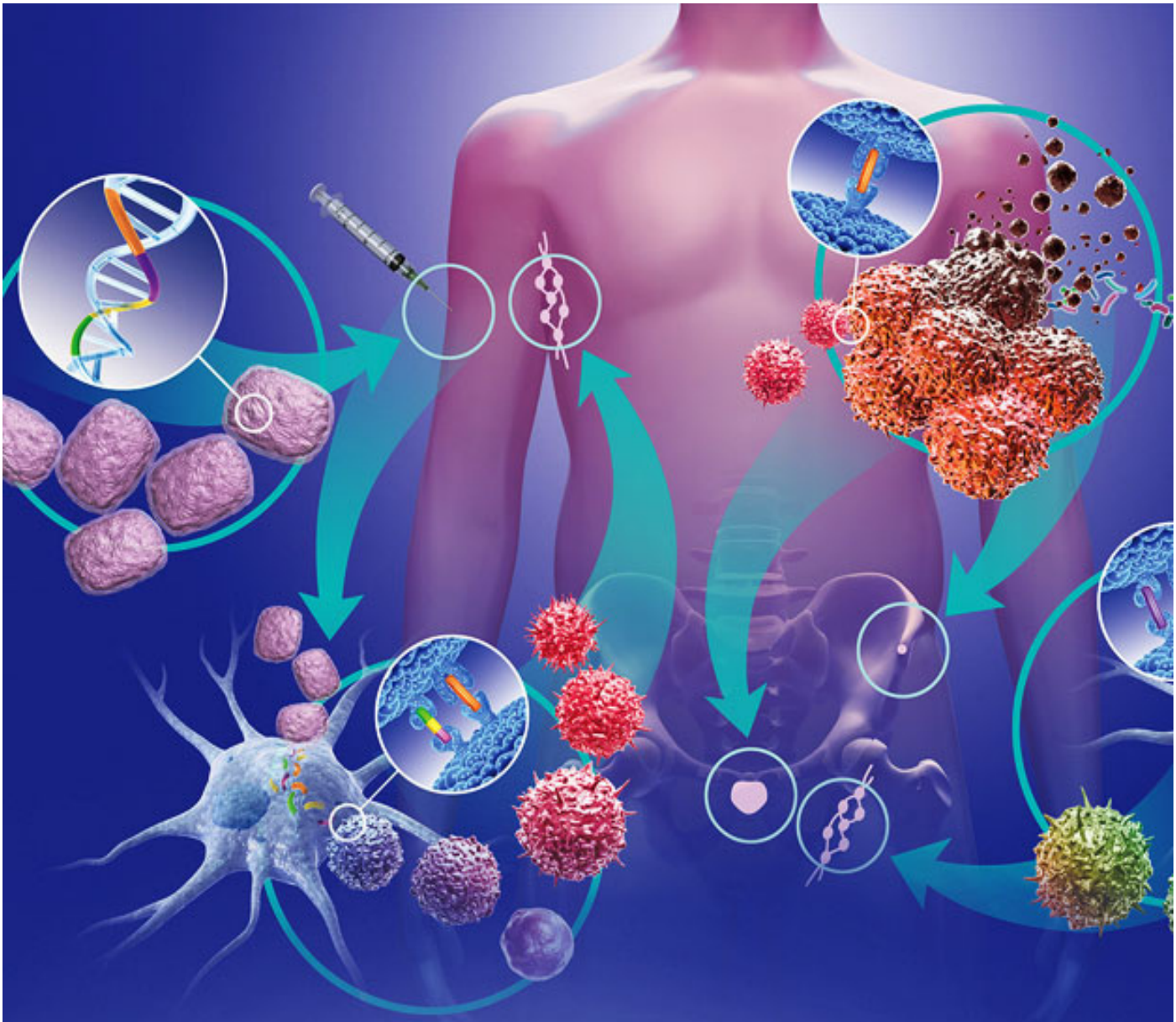

CANCER THERAPY

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How to Fight Cancer: An Outlook

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Background

Cancer

Cancer is an abnormal cell growth (see Figure 1) where cells tend to proliferate in an uncontrolled way, loss their normal function and can spread through blood at all the body [1-3]. There are more than 200 types of cancer, each with different causes and symptoms. Personal risk of developing cancer depends on a variety of factors including age, lifestyle and genetics.

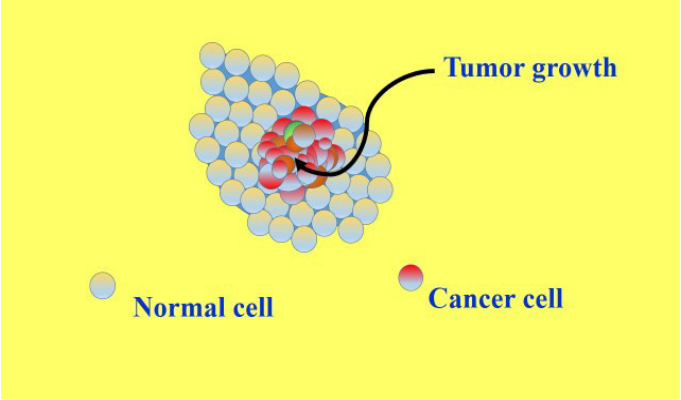

Figure 1: A tumor growth.

Cancer mortality

As illustrated in **Figure 2, c**ancer is the 2nd most common cause of death in the globe [4]. In 2015, from a total of 15.2 million cancer case 8.8 million cancer related-death were recorded [5]. In 2018, 18.1 million cancer cases and 9.6 million related-deaths were recorded. One in five men and one in six women worldwide develop cancer and one in eight men and one in eleven women die from cancer [4]. By the year 2035, it is expected to affect 24 million and to kill about 14.6 million [5]. Nearly, three quarters of tumor-linked deaths are associated with Developmental Countries [6]. In Egypt, World Health Organization announced 72,300 cancer related death (39,300 from males and 33,000 from females) in the year 2014. That represented about 14% of the Egyptian total deaths recorded in the same year [7].

In 2018, lung cancer is the most commonly diagnosed cancer with 11.6% from total cancer cases and the leading cause of death with 18.4% from cancer-related deaths in both genders, followed by female breast cancer with 11.6%, prostate cancer with 7.1%, and colorectal cancer with 6.1% for occurrence, and colorectal cancer with 9.2%, stomach cancer with 8.2%, liver cancer with 8.2%, breast cancer with 6.6% and esophagus cancer with 5.3% for cancer-related deaths [4]. Between 70% and 90% of common cancers are due to environmental factors [8]. Between 30% and 50% of cancers can now be prevented by avoiding risk factors and applying current prevention approaches [6].

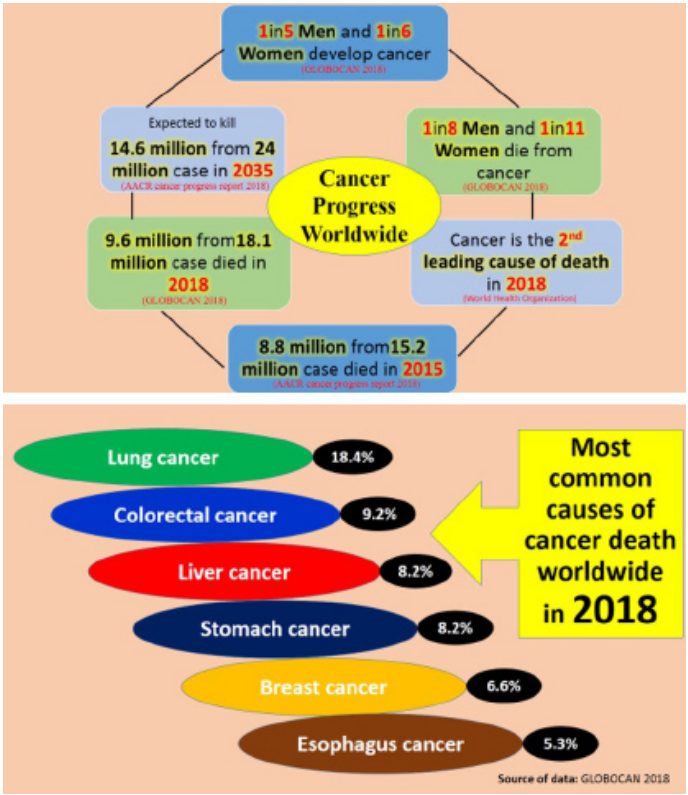

Figure 2: Cancer-related deaths.

Cancer causes and risk factors

Causes and risk factors of cancer development are highly variable. They include for example tobacco, sunlight, radiation, alcohol, infection, medications, etc. Poor/unhealthy diet and tobacco smoking may participate to approximately 35% and 30%, respectively of all cancers. They represent the most cancer causes associated with the highest-risks related to cancer [9] **(**see **Figure 3)**.

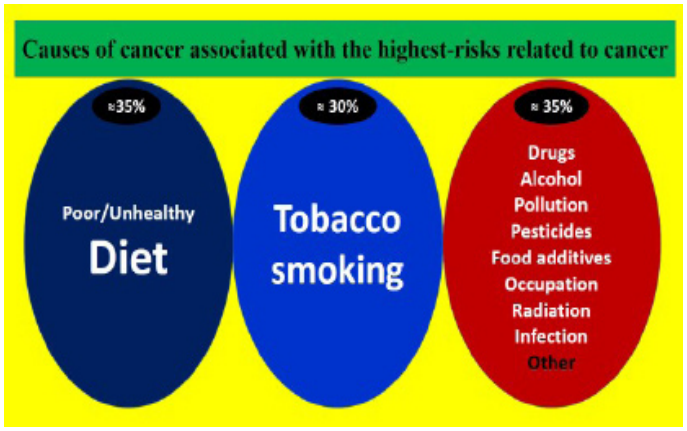

Figure 3: Causes of cancer associated with the highest-risks related to cancer. Numbers (%) are cited from reference [9].

Cancer propagation theories

There are two main cancer propagation theories (models): The stochastic (classic) and cancer Stem Cell (CSC, modern). In the stochastic theory, every cancer cell in a tumor could gain the ability to self-renew and differentiate to the numerous and heterogeneous lineages of cancer cells that compromise a tumor so all undifferentiated cells have similar possibility to change into a tumorigenic cell [10].

Cancer Stem Cells (CSCs) were first identified by John Dick in acute myeloid leukemia in the late 1990s. The first conclusive evidence for CSCs came in 1997 during working on a hematological tumor (leukemia). The first evidence of a solid tumor cancer stem-like cell followed in 2002. CSCs have two defining features: (1) Their long-term ability to self-renew and (2) Their capacity to differentiate into progeny (daughter cells) that is non-tumorigenic but still contributes to the growth of the tumor. Origin of CSCs is not confirmed yet only postulations are introduced. Postulations comprise mutations either in developing stem, progenitor cells, adult stem cells, adult progenitor cells, or mutant differentiated cells that acquire stem-like aspects. Usually, markers specific for normal stem cells including CD133, CD44, ALDH1A1, CD34, CD24 and ESA are frequently used in CSCs isolation from tumors [11]. In the CSC theory, it is assumed that only the CSCs can generate a tumor because of their self-renewal and proliferative properties (**Figure 4**) [12].

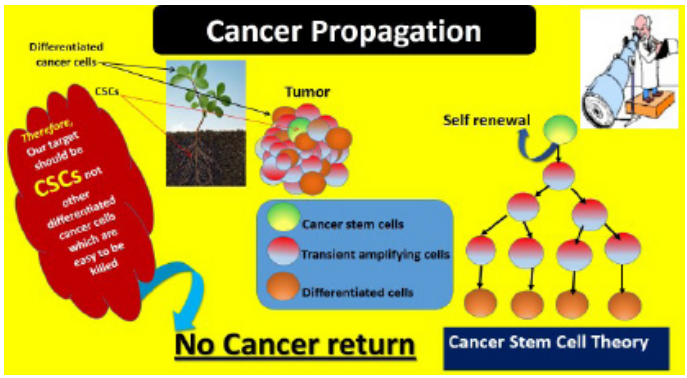

Figure 4: Cancer propagation based on cancer stem cell theory, and how it could be benefit in cancer treatment. In the cancer stem cell theory, only the CSCs have the ability to generate a tumor.

Cancer diagnosis

Cancer can be diagnosed through biopsy, imaging techniques, and laboratory serological tests.

Cancer treatment

Surgery, chemotherapy, and radiotherapy are the standard methods used to treat cancer but they are usually of high cost and have serious adverse effects with restrictions of their use [13].

Thus, there is an accelerated need for efficient, low-cost and more-safe treatments with acceptable minimal adverse effects.

How to fight cancer

Firstly, there are some issues associated with normal individuals including: (1) To keep good health, (2) To use anti-cancer diet to reduce risk for developing cancer and (3) To keep continual routine medical checkup that helps to discover cancer incidence early if developed that's will ease its treatment and complete recovery.

Anti-cancer diet

To reduce risk for developing cancer, using anti-cancer diet is a good strategy. The American Cancer Society suggested you to eat five servings of fruits and vegetables daily as a minimum with your eye on keeping a healthy weight. Scientific researchers found that certain foods (see **Figure 5**) could fight cancer or at least reduce the risk for developing cancer. Researchers and experts assume that diet rich in vegetables and fruits contain phytonutrients that are good antioxidants can protect against oxidants-tissue damage, and anti-inflammatory can prevent inflammation. Thus, they may protect healthy persons from developing cancer or may slow cancer growth rate in cancer patients [14].

In fact, there is no guarantee for cancer preventing by eating these recommended cancer-fighting foods but they will help to decline the incidence risk.

Figure 5: Some of the recommended cancer-fighting foods.

Take these anti-cancer diet guidelines in your consideration [15]:

Eat fruits and vegetables for snacks: Fruits and vegetables are rich in vitamins and nutrients that are supposed to decrease the threat of developing some cancers. Pay particular attention to plant-based foods, including fruits and vegetables, whole grains, legumes, and nuts, and mostly use olive oil instead of butter and fish instead of red meat.

Drink green tea throughout your day: Green tea is a strong antioxidant may be helpful in preventing liver, breast, pancreatic, lung, esophageal, and skin cancers. Epigallocatechin-3 gallate is one of the green tea active constituents. Epigallocatechin-3 gallate can prevent cancer via blocking the essential urokinase enzyme for cancer growth.

Eat more tomatoes: It contains high amount of carotenoid lycopene. It was evidenced that lycopene is more powerful antioxidant than beta-carotene, alpha-carotene, and vitamin E. Lycopene protects against certain cancers such as prostate and lung cancer. Cooking tomatoes releases the lycopene and makes it available to the body.

Olive oil: Use it widely for both cooking and salad oil. Breast cancer rates are 50 % lower in Mediterranean countries that widely use olive oil than in USA.

Eat grapes: Red grapes have seeds filled with the super-antioxidant activin. Activin also found in red-grape juice. It defends against certain types of cancer.

Abundantly use garlic and onions: They have active sulfur compounds that prevent cancer. It was established that garlic and onions can inhibit formation of powerful carcinogens nitrosamines that target the colon, liver, and breast.

Eat fish: Fatty fish contain omega-3 fatty acids. They reduce the risk of prostate cancer.

Cancer therapy

Secondly, there are some issues associated with specialists in the field of cancer. If you have cancer (cancer already developed), searching for efficient and satisfied treatment (therapy) for both patients and clinicians (doctors) is urgent. To achieve this big goal, interested researchers should work on three levels; (1) Pre-therapy to clearly understand the causatives of cancer and carcinogenesis process, (2) Therapy to select the best among clinically approved therapeutics and to discover new better natural/seminatural or synthetic ones with no or minimal adverse effects on healthy cells and to test them as a pre-step towards their approval in the nearest future, and (3) During/post-therapy to treat side effects of already clinically approved therapeutics by adding ones (**Figure 6**).

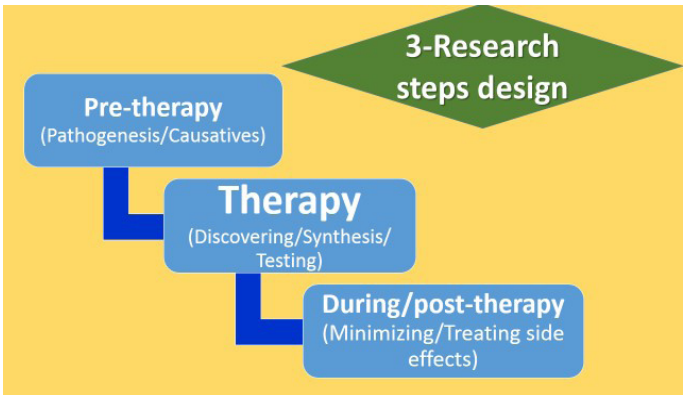

Figure 6: A three-research steps plan for efficient and satisfied cancer treatment.

(1) Pre-therapy

To fight cancer causatives is another strategy to fight cancer. Researchers' deep understanding of cancer causatives and risk factors and how these can cause or progress to develop cancer and transferring this information in a simple way to normal people can help (**Figure 7**).

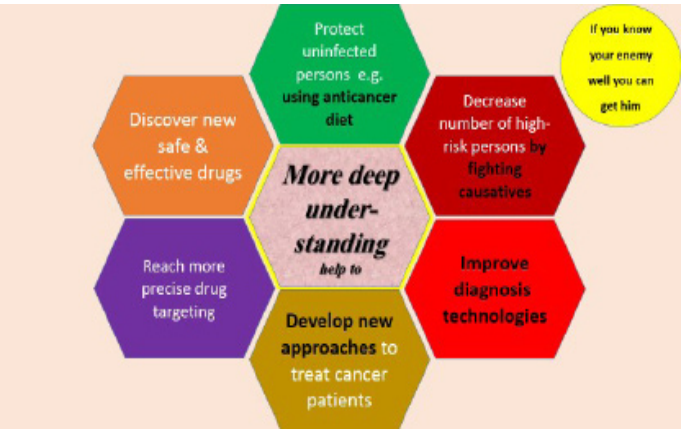

Figure 7: Researchers' deep understanding can help in fighting cancer.

People knowledge of cancer causatives help them to avoid exposure. Also, knowing how to protect themselves is of great importance. This contributes in decreasing the number of high-risk cases.

For example, obesity is a chronic disease of multi-factorial origin that develops from the interaction of social, behavioral, psychological, metabolic, cellular, and genetic factors. It is the condition under which adipose tissue is increased and can be defined as an increase in body weight that results in excessive fat accumulation [16]. **Figure 8** simply explains how obesity (overweight) could put you in a risk for cancer development. This understanding encourages people to try hard to keep a healthy weight to avoid this risk.

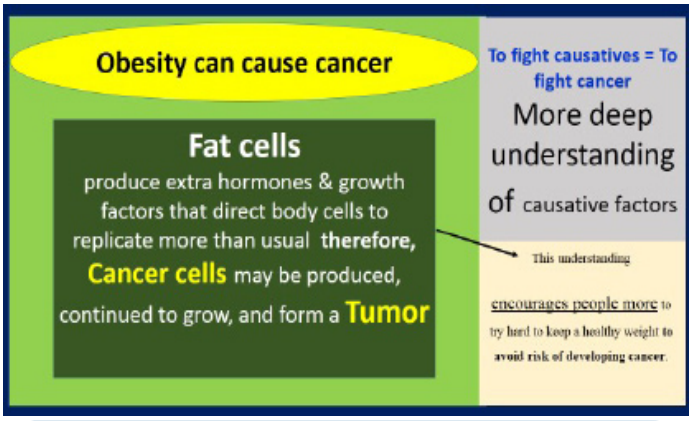

Figure 8: Avoiding obesity may help you prevent cancer develop.

Moreover, the next generation of diagnostic technologies that are moving rapidly from the bench to the bedside has the power to fundamentally change cancer treatment in the future.

For example, recent studies have shown that it is possible to use a blood sample, or liquid biopsy, rather than a traditional tissue biopsy, to obtain material that can be analyzed to provide information about the molecular alterations associated with a patient's cancer. Liquid biopsies have the potential to modify early detection, diagnosis, treatment, and surveillance of cancer by identifying markers of disease, therapeutic response, resistance, and recurrence [5].

Another example, hepatitis C virus (HCV)-cirrhotic patients have the highest threat of developing hepatocellular carcinoma (HCC) and may be at risk of extra hepatic cancer. A recent study focused to use CSCs markers in diagnosis. It was planned to investigate CSCs markers (CD133 and CK19) in HCV (genotype-4)-cirrhotic Egyptian patients with/without HCC or extra hepatic cancer, to assess the degree of their correlation with cell cycle abnormalities and finally to assess the role of their combination as diagnostic tool for discrimination of cirrhotic patients with HCC from those with extra hepatic cancer. The study showed that a panel contains CD133 with G2/M and CK19 is an excellent diagnostic tool (AUC = 0.978 and accuracy = 92.5%) for differentiation of HCV-cirrhotic patients with HCC from those with extra hepatic cancer [17].

Furthermore, deep understanding of the mechanism of proliferation and differentiation of normal Stem Cells (SCs) from different sources before and after their engraftment during cell-based therapy aid in improving this type of cancer treatment and its outcomes.

In this regard, a recent study aimed to demonstrate the fate of human olfactory bulb neural stem cells (hOBNSCs). Their possible ability to proliferate and differentiate into different neurons, oligodendrocytes and astrocytes through monitoring changes in expression profile of proliferation (NES, NR4A1, SOX2, MSI1) and differentiation (FOXO4, CSPG4, MAP2, GFAP)-related genes were assessed. Among the differentiated cells, GFAP-expressing astrocytes comprised the highest population of cells. CSPGS-expressing immature oligodendrocytes comes in the second order followed by MAP2-expressing immature neurons and FOXO4-expressing mature oligodendrocytes. These data will help researchers to expand their understanding about the mechanism of proliferation and differentiation of hOBNSCs [18].

(2) Therapy

The next generation of therapeutic technologies also has the potential to fundamentally change cancer treatment in the future [6].

Great efforts have been made to develop novel antitumor drugs to replace the current clinically approved ones because of their serious side effects and high cost. More than 70% of the studied anticancer agents are either natural products, or natural product-derived substances such as alkaloids, tocopherols, anthocyanins, flavonoids, etc. [3]. Among the studied chemically synthesized compounds with antitumor potential, transition-metal complexes, based on the assumption that endogenous metals may be less toxic [19,20], and organic compounds with biological activities such as caumarines, quinoxalines, benzothiazoles, etc [3,13].

In continuation of these efforts, in our lab, a group of different newly synthesized compounds with potential anticancer activity were studied. Among them, three different Iron(III) complexes; Iron(III) diacetylmonoxime-2-hydrazinopyridine [2], Iron(III) 3-oxo-N-(pyridin-2-yl)butanamide [8], and Iron(III) rifampicin [21] showed appreciated antitumor activities in vitro and in vivo against EAC. The three complexes displayed dose-dependent antitumor effects with minimal toxicity towards healthy tissues. At a dose of 1/10 of LD50, the first complex showed almost analogous but the second complex showed better efficiency than the reference drug cisplatin. Compared to pure rifampicin, Iron(III) rifampicin complex was more potent in holding back the tumor progression. Iron(III) rifampicin complex (at a dose of 1/20 of LD50) showed a bit better antitumor activity than cisplatin.

Also, Cobalt(II) diacetyl monoxime-2-hydrazinopyridine [19]

and nickel(II) diacetyl monoxime-2-pyridyl hydrazone [1] complexes can be considered as potent anticancer agents with minimal side effects. Each of them exhibited a significant antitumor activity in EAC-bearing mice that was nearly comparable to that of cisplatin for Co(II) complex while it was stronger than that of cisplatin for nickel(II) complex.

In addition, a series of new complexes of V(IV), Ru(III), Pd(II), Pt(II) and Ag(I) derived from 2-hydrazinobenzothiazole have been synthesized and their anticancer activities have been investigated against EAC and human cancer cells (Hep-G2, MCF-7 and HCT-116) and complex (5; Ag(I)) showed the highest activity [20].

Furthermore, a novel synthetic flavonoid ''ethyl 2-amino-4-phenyl-4H-benzo(h)chromene-3-carboxylate'' was synthesized, and investigated in vitro for potential antitumor activity in compare to that of the well established antitumor natural flavonoid ''quercetin''. The new compound displayed potent optimistic antitumor activity against PC3 and Hep-G2 cells [3].

Problems of currently used cancer therapy are tumor return as a result of bad cancer targeting and serious side effects that arise from affecting healthy cells besides cancer cells. Selective targeting of Cancer Stem Cells (CSCs) may offer a good solution for these problems. It may minimize anticancer drug induced side effects, ensure tumor regression, and prevent tumor relapse (**Figure 9**).

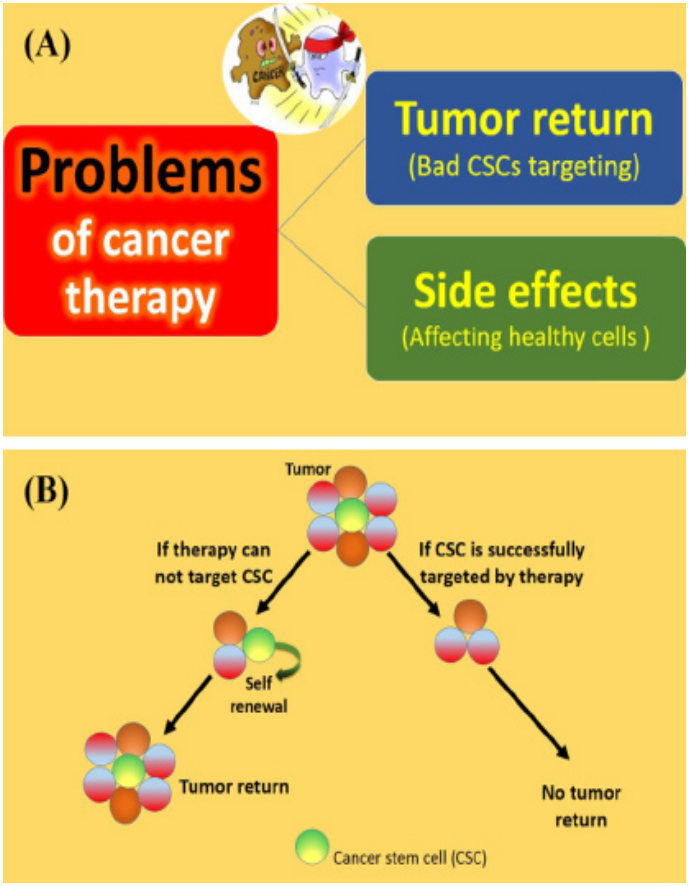

Figure 9: Main cancer therapy problems (A), and selective targeting of cancer stem cells (B).

In this regard, using nano-technology may be successful in improving performance of the currently used cancer therapy. Nano-particles (1–100 nm in size) can interact uniquely with bio-molecules and may aid in cancer treatment [22]. Many polymeric nano-carriers such as polylactic acid (PLA), polyglycolic acid (PGA) and Polylactic-co-glycolic Acid (PLGA) have been synthesized in the last few decades to act as delivery vehicles for chemotherapeutic medicines [23]. It can significantly increase the anticancer efficiency of both currently used and new chemotherapeutic drugs and increase patient satisfaction. Nano-particles of sizes 5 to < 200 nm are not able to exit the intravascular space in normal tissues, while they are capable to readily exit leaky tumor-associated vessels [24]. This ensures targeting tumors and limits drug delivery to healthy tissues thus minimizes side effects.

Lately, in our lab, we established that targeting cancer cells with the new compound *N*-butylpyridoquinoxaline 1,4-dioxide (NBPQD)–PLGA nano-particles rather than free NBPQD results in much better cancer cells toxicity and enhances more apoptotic tumor cellular death. Our study results not only indicate that utilization of NBPQD–PLGA delivery system improves NBPQD anticancer efficacy but also indicate it alters the anticancer potency pattern [13]. We also investigated the anticancer activity of another drug delivery system consisting of poly (L-lactic) acid/Pluronic® F-127 (PLLA/PF127) loaded with NBPQD or 2-amino-3-cyano-6-methylquinoxaline 1,4-dioxide (ACMQD) on cancer cell models. PLLA/PF127-NBPQD and PLLA/PF127-ACMQD nanofibers showed higher in vitro anticancer activity towards all investigated cell lines compared to free NBPQD or free ACMQD. PLLA/PF127 nanofibers with NBPQD or ACMQD increased anticancer efficiency through activation of a p53 and p21 apoptotic-signaling pathway [25].

Based on the modern CSC theory of cancer propagation selective targeting of CSCs not other differentiated cancer cells, which are easy to be killed, will ensure tumor regression, and prevent metastasis and relapse (see **Figure 9** above). Looking to the future, we hope that we and other interested researchers work hardly to participate in this promising area in our coming investigations.

(3) During/post-therapy

In this stage, more concern is directed to cancel/minimize cancer drug side effects. That could be achieved for example through using adding ones such as protective natural supplements or through using normal stem cells.

A recent study [26] suggested a promising clinical use of mesenchymal stem cells (MSCs) (**Figure 10**) along with cisplatin during cancer treatment to prevent renal damage due to its ability to renew damaged kidney cells. Another recent study suggested aqueous extract of *B. sacra* as a potent nephro- and hepato-protective in rat model [27].

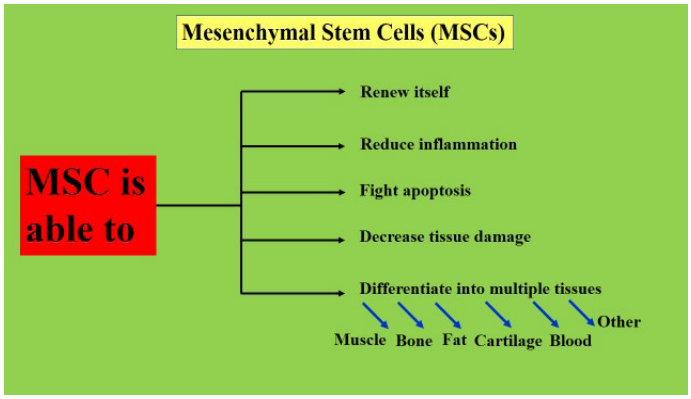

Figure 10: Mesenchymal stem cells.

Conclusion

Cancer represents a main medical public health problem but really, there is hope that progresses in preventing, diagnosis, and clinical treatment strategies of cancer could be achieved in the near future. Appreciated efforts are going on. Finally, as long as there is a life, there is always a hope.

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