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Which Hypothesis Best Explains the Development of Cancer?

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Abstract

There are three theories of cancer development analyzed in this review. The first theory is the immunological theory, which states that cancer is a result of the immune system failing to detect a cancerous cell in which results in uncontrolled cell growth. The second theory is the somatic mutation theory, which states that genetic mutations are a direct cause cancer. The third theory is the stem cell theory which states that cancer results from an uncontrolled stem cell. The difference in each theory helps guide a clinician's judgment in how to treat cancer. If a clinician believes in the immunological theory, he/she will view the best route of treatment as being by targeting the patient's immune system. One who believes somatic mutation theory would say that the patient's genetic makeup of the patient is the ideal target for treatment. One who believes in the stem cell theory would say that the only method of treatment is to remove the cancer entirely as any residual cancer will return. Based on all the evidence it appears that there is not one individual factor that causes cancer development, rather it is a combination of several factors that result in cancer.

Introduction

In 2013 cancer was reported to affect over 1.6 million people (Siegel, et al., 2013). Despite cancer being such a highly discussed and researched disease there are many things that remain unknown. One of the major debates is how cancer develops; there are three major schools of thought: the immunological theory, the somatic mutation theory, and the stem cell theory.

The immunological theory postulates that cancer develops as a result of the immune system failing to detect the cancerous cell. As a result of an undetected cell the cancer grows at an uncontrolled and dangerous rate, thereby damaging the host. If this is the sole etiology of cancer, the immune system could be harnessed to treat a person who had developed cancer. For example, a new cancer vaccine has been developed for prostate cancer patients. This vaccine was developed for two reasons. Firstly, prostate cancer cells have several tumor-associated antigens. Secondly, because the prostate is a nonessential organ, annihilation of any normal prostate tissue that comes about because of the immune response has no clinical consequence (Singh & Gulley, 2014). While not all cancers have these qualifications that make them susceptible to a vaccine, other forms of immunotherapies are in development to try and take advantage of the specifics of each cancer to attack it immunologically.

The somatic mutation theory postulates cancer develops due to a genetic mutation leading to uncontrolled growth. A study showed that there are specific gene mutations involved in breast and ovarian cancer. These are mutations of either the BRCA1 or BRCA2 gene (Miki, et al., 1994). More specifically, it has been shown that women with BRCA1 mutation by age 80 have a 72 percent chance of developing breast cancer. While women who have the BRCA 2 mutation have a 69 percent chance of developing breast cancer (Kuchenbaecker, et al., 2017). Treatments based on this theory focuses more on the genetics of a person and using that field as a method to control or treat the cancer.

The stem cell theory of cancer assumes that cancer develops because there is an uncontrolled stem cell in the body. All humans develop from stem cells that multiply repeatedly. However, during human development stem cells become specialized and eventually stop multiplying. This theory of cancer development says that cancer results from a stem cell that has not "turned off", resulting in uncontrolled growth to the point of being detrimental to the host. This theory has many implications. Some clinicians evaluate a cancer treatment based on how much it causes the tumor to shrink, but without removing the source the tumor will come back very quickly because the stem cells are still there. Physicians and Oncologists who subscribe to the stem cell theory may treat cancers differently than those who believe in the immunological theory or the somatic mutation theory.

The significance of each theory is that the information regarding how the disease develops can help determine the best course of treatment. Evidence seems to point to all three of these theories, hence there is no conclusive explanation. This review will examine all the evidence in order to determine which hypothesis best explains the development of cancer.

Methods

The articles and journals used in this review were found on PubMed, Ebsco, and Google Scholar. These articles were carefully reviewed in order to determine their relevance to the thesis.

Discussion

Immunological Theory of Cancer

This theory has been associated with three general steps the body constantly goes through: elimination, equilibrium and escape. The elimination step consists of the immune system surveying for all cancerous cells and destroying them. However, there are times when tumorous cells remain undetected while remaining dormant. This period is defined as equilibrium because there are cancerous cells in the body, but they are not doing any harm. The final step is escape in which the tumor gains dominance over the immune system and starts spreading (Lopez, et al., 2016). This implies that the immune system's activity and

ability to detect cancerous cells is important before the cancer gets out of hand.

To try to determine how immune activity affects cancer, residents of Japan, mostly above 40, were given a questionnaire that covered 90 lifestyle factors. People who participated in the study gave a peripheral blood sample after fasting for over 12 hours. A follow-up was performed 11 years later where cancer incidence and death totals were gathered. Based on the questionnaire, each patient was assessed for cancer risk at one of three levels, low, medium, or high. Of the 8552 individuals who took the survey, 211 of the 3625 whose blood was sampled were identified as cancer cases. A number of the cases had to be excluded based on age, blood samples being inaccessible, etc. The total number of cases remaining was 154, 92 men and 62 women. Accounting for age, it was found that patients with lower cytotoxicity activity, were at a significantly higher risk for developing cancer when compared to those with medium or high activity (Imai, et al., 2000). This study points to the fact that cytotoxic activity can help a person fight cancer, further illustrating that the immune system plays a role in cancer treatment.

A specific type of immunotherapy is currently being developed in which some of the patient's T-cells are extracted and modified to become chimeric antigen receptor t-Cells (CAR-T cells). These T-cells are then given artificial receptors that are from monoclonal antibodies which allow the CAR-T cell to bind to the cancer cells. The patient is then treated with chemotherapy to eliminate any immunosuppressant activity in the body. The CAR-T cells are then injected and are free to attack the cancer cells. This treatment sounds perfect but there are some complications that arise. Cytokine release syndrome (CRS) is a life-threatening complication in which the immune system goes into a state of being overly active and releases an excessive number of cytokines which results in organ toxicity. CRS is manageable but one has to be conscious of it when treating a patient with CAR-T. Another complication that can arise is CAR-T cell related encephalopathy syndrome. This syndrome can result in some patients feeling slightly disoriented while others can have seizures (Graham, et al., 2018). This methodology of cancer treatment is new but is showing great promise. It shows that the immune system, under careful monitoring, can be harnessed to fight cancers.

A person's immune system doesn't allow cancer cells to grow because the natural killer cells, or NK cells detect the cancers and kill them. These cells can identify a cancerous cell because they identify which cells are "not self" cells by searching for specific receptors that only one's own cells have. Therefore, they find the cancer cell and kill it before it starts growing. Although some cancer cells go undetected, there are researchers who believe that the NK cells can be used to kill an active cancer. A new treatment is being studied in which NK cells are being combined with the concept of CAR-T cells creating CAR-NK cells. These cells have several advantages over CAR-T cells. Firstly, because NK cells have natural receptors for tumors, they have an easier time identifying cancer cells even if the CAR portion of the cell is downregulated by the cancer. Secondly, CAR-NK cells do not undergo clonal expansion or immune rejection thus eliminating the issue of cytokine release syndrome that is present with CAR-T cells. Lastly, HLA matching is not necessary for CAR-NK cells, which means the graph-versus-host disease is not an issue when it comes to CAR-NK cell treatment. Currently there is not enough clinical data to fully implement the treatment, however, there are studies being performed to help investigate new treatment options. For example, CAR-NK cells are being researched to help determine their ability to fight hematological and solid tumors, including glioblastoma, prostate cancer, and ovarian cancer (Hu, et al., 2019). While this treatment is in very early stages it has had great results thus far. If this treatment can prove to be effective it can have massive implications in the successful treatment of cancers because there are few side-effects.

Dendritic cells are another one of the immune cells being used to fight cancer. Dendritic cells function as an antigen presenting cell meaning, when it recognizes an antigen it alerts the body to produce antibodies. There are vaccines that have been proven to work that are prepared by removing a patient's dendritic cells and "teaching" them to recognize cancer cells, then reinjecting them into the patient. Once these dendritic cells are in the bloodstream, they can identify the cancer cells and initiate a T-Cell response to them. However, there were several issues when the dendritic cells were taken from ex vivo and put inside patients. Firstly, some patients experienced a T-cell response from the injection, but it did not result in significant improvement. This alteration in functionality could be a result of the cells being transferred from an in vivo environment to an ex vivo environment, then returned to in vivo. Another issue with the vaccine is that the process is very time-consuming and expensive. Lastly, the dendritic cell vaccine is reliant on the patient's immune system and its function. Because of this, in vivo preparation of the dendritic cell is still being perfected (Le Gall, et al., 2018). This technique can be very helpful to cancer patients as often the cancer proliferates because the immune system fails to recognize the cancer cells. With this treatment the incidents of cancer cells going

undetected can be virtually eliminated resulting in the body halting the cancer cells growth.

Another form of immunotherapy using dendritic cells is called dendritic-cell cytokine induced killer cells (DC-CIK). In the study, there were several criteria that had to be met when determining who was an appropriate candidate. The first requirement was that the patients had to have advanced cancer (stages 3-5). Secondly, prior to this study, patients had to have received first-line treatment, including surgery, adjuvant chemotherapy and/or radiotherapy. The study examined a total of 142 patients with histologically confirmed colorectal carcinoma, 71 were treated with DC-CIK and 71 were not. Patients were examined at three separate times, after 1, 3 and 5 years. The retrospective study found that patients who were treated with DC-CIK had 1,3 and 5-year prolonged progression free survival and overall survival versus those who were not treated. Minor side-effects were experienced by the patients treated with DC-CIK such as mild fever, chills, fatigue, while three also developed a headache and one developed chest tightness and hypotension. While these symptoms cannot be ignored, in the grand scheme of cancer treatment these side-effects are very mild. This study shows the effectiveness of DC-CIK and its ability to combat colorectal cancer in patients who were treated with first-line treatments (Xie, et al., 2017). While this study has its limitations because it required first line treatment such as surgery, it does provide a powerful tool for patients who have already gone through or may require first line treatments.

The examples listed above all seem to point to the accuracy of the immunological theory of cancer. Perhaps the most indicative proof that cancer prevention is a function of the immune system is from a study performed several years ago which analyzed 12 patients with glioblastoma who received regular course of immunotherapy (a dendritic cell vaccine). However, a few patients were also given a tetanus vaccine. The patients who were given the immunotherapy and the tetanus vaccine lived between four to eight years after their treatment. The patients who received the immunotherapy with another placebo drug lived only 11 months following their treatment (Mitchell, et al., 2015). The reason the tetanus shot impacts the cancer defense is because once given, the body begins to create t-cells as a typical reaction to a vaccine. Due to this additional t-cell production the body was more prepared to fight the cancer as well (Haelle, 2015). While this study was performed on a small sample size the results point to the same conclusion as the previous studies; it illustrates the role the immune system plays when fighting cancer.

These are just some of the treatments in development, all working under the assumption of the immunological theory of cancer being correct. As it stands, the treatments appear promising and with further research they can hopefully be perfected and cancer patients can be cured with minimal side effects. All the studies cited point to the immunological theory of cancer as a very real and likely explanation for cancer development.

Somatic Mutation Theory of Cancer

The somatic mutation theory analyzes the development of cancer by looking at genetic factors. The specific genetic variances in squamous cell carcinoma (SCC), adenocarcinoma (AC), and adenosquamous carcinoma (ASC), 3 types of cervical cancers, were analyzed. Three hundred and one patients with SCC, AC, or ASC who were all treated with radical hysterectomy with lymphadenectomy as their primary treatment were analyzed. All follow-up data was obtained 5 years after primary treatment. One hundred and sixty-six (55%) of the patients had SCC, fifty-five (18%) had AC and eighty (27%) had ASC. In 103 of the tumors there were 123 somatic mutations detected as roughly 4% of the tumors had multiple mutations. The specific mutations were identified for each cancer. The PIK3CA was most common in SCC and ASC while KRAS was most common in AC. However, in each type of cervical cancer there was not only one mutation rather there were several mutations found across multiple genes such as, PTEN, PPP2R1A, CTNNB1, CDKN2A, FBXW7, FGFR3, NRAS, and HRAS. The KRAS mutation is not exclusive to cervical cancers as it has also been linked to colorectal, lung and pancreatic cancers. KRAS and PIK3CA mutations were both not associated with survival; however a clear trend of lower survival rate was in patients carrying a PIK3CA mutation (Spaans, et al., 2015). This study points to a connection between specific cancers and mutations that result in them. If an unknown cancer's genetic sequence could be inspected it could give a clinician a clear idea of what cancer he/she is dealing with and how to properly treat that patient.

Cervical cancers are not the only cancers to have a gene associated with them as prostate cancers were also found to have specific genes connected to them. These genes were identified by looking at a prostate specific antigen (PSA) a protease produced in the prostate, as well as prostatic acid phosphatase (PAP). By looking at these two markers the researchers used the technique of guilt-by-association which works based on combinatoric measure of association. Forty-thousand different genes were analyzed, and each gene was determined to be present in prostate cancers if the cDNA corresponding to that gene is detected in the library. Upon analysis of all

40,000 genes most of them were determined to not be related to prostate cancer. However, eight of the genes were identified as being associated with it (Walker, et al., 1999). The extent of their association is difficult to prove because correlation is more provable than causality, but the association is significant none the less.

Certain genes have been identified as being related to breast cancer that is metastatic to bone. One hundred and seven breast cancer patients who had developed metastasis had their negative-lymph nodes biopsied. Sixty-nine of the relapses were categorized as bone while 38 were labeled as not bone. Upon analysis, 69 significantly unique gene sets were discovered across bone and non-bone samples. The five most common genes in bone cancer were TFF1, TFF3, AGR2, NAT1, and CRIP1. TFF1 was studied in 122 independent breast tumors in node-negative patients which indicates it is the most prevalent mutation. The researches then attempted to predict a correlation between a cancer's gene sets and that cancer spreading to the bone. The samples were divided into a test set and a training set. Five hundred and eighty-eight genes were selected and subjected to PAM analysis. A 31-gene predictor was selected after 10-fold cross validation that could identify relapse to the bone at 100% sensitivity and 50% specificity. The predictor showed 79.3% positive predictive value and TIFF1 was present in the gene list. Two random gene sets of 50 and 100 genes were analyzed to test the validity of this method. Twenty-nine of the 50 random genes showed 100% sensitivity and of these 29, the average specificity is 13.2% which indicates that the 50% specificity found by the earlier gene list is significantly higher than a random gene set. Based on SAM sets the researchers determined that the most common genes associated with the cancer metastases were TFF1 and TFF3. TFF3 was also found as overexpressed in some metastatic prostate cancers, while TFF1 was found to induce cellular invasion of kidney and colon cancer (Smid, et al., 2006). This further proves that there is a strong tie between cancer and genetics.

In high-grade serous ovarian cancers, triple-negative breast cancers, esophageal cancers, small-cell lung cancers, and squamous cell lung cancers, the p53 gene is mutated in at least 80% of patients' tissue samples (Duffy, et al., 2017). P53 has two major functions in the cell cycle thereby linking it to cancer. P53 serves as a cell cycle regulator, so if the cell no longer needs to go through the cell cycle p53 will stop the cycle. Another function is that a normal p53 protein stops a cell that has already grown too much and is technically cancerous by initiating apoptosis for that cell (Zilfou & Lowe, 2009). When p53 is mutated the cells experience uncontrolled growth either because its cell cycle is not arrested or because a cell that is already out of control is not sent to apoptosis.

Because of the prevalence of mutant p53 in cancer patient's researchers have looked into a way to stabilize these mutant forms of p53. They analyzed mice whose p53 proteins were removed by one of several methods. One method was that the mice were injected with an anti-p53 antibody in which the p53 proteins in the mice underwent ubiquitination. Another method was by using an adenovirus, either Ad/GFP (green fluorescent protein) or Ad/His. They found that when these mice were exposed to a drug called CP-31398, not only was the DNA binding activity of mutant p53 restored thus allowing cell cycle arrest and induction of apoptosis, but it can also increase the steady-state levels of wild type p53 (Takimoto, et al., 2002). Another study showed that CP-31398 also inhibited the ubiquitination of p53 proteins. A non-small-cell lung carcinoma cell, H460, was exposed to CP-31398 for an hour, it was then exposed to ALLN, a proteasome inhibitor, for four hours. Another group of cells was exposed to ALLN alone and both were analyzed. The results showed that the cells that had just been exposed to ALLN showed a typical pattern of ubiquitinated p53 ladders. However, the cells treated with a mixture of CP-31398 and ALLN or just CP-31398 alone showed no ubiquitinated p53 ladders (Wang, et al., 2003). These two applications of CP-31398 demonstrate how useful it can be in preventing cancer because of the prevalence of p53 mutations in cancer patients.

Another protein that has been a target for treatment is p21, a cell cycle inhibitor, cell proliferation effector, and apoptosis regulator. As with p53, many cancer patients have been shown to have their p21 proteins mutated. Gene editing techniques such as CRISPR, TALEN's, ZFN's and rAAV have all been used to change p21 expression and have been shown to suppress tumorigenesis phenotypes and reduce drug resistance. Several chemical treatments target p21 as well. Histone deacetylase inhibitors help increase the expression of p21. Trichostatin A, PAC-320, and HDAC inhibitor combined with bortezomib or doxorubicin, have shown to enhance p21 expression in pancreatic cancer, prostate cancer and ovarian cancer respectively (Shamloo & Usluer, 2019). All these treatments targeting p21 can have massive ramifications because of p21's effect on cell cycle arrest.

Specific genetic mutations are directly linked to specific cancers which seemingly indicates that certain genetic mutations are linked to specific cancers, thus

legitimizing the claim that cancers have genetic components to them.

Stem Cell Theory of Cancer

This theory assumes that cancer is a result of a stem cell that is unregulated and grows uncontrollably. Because of several unique characteristics of prostate cancer such as histological heterogeneity, metastatic growth, drug resistance, and distant relapse after effective primary treatment, the stem cell theory was proposed as a possible explanation for prostate cancer. It was tested by searching for stem cell markers in the cancerous tissue. While there is not one marker specific for prostate cancer stem cells, there are a few methods used to help identify the stem cells such as: β1 integrins, CD133, CD44, stem cell antigen 1 and the ABCG2-associated drug-resistance proteins. β1 is a marker for "stemness" because it is essential for sustaining a functional stem cell population and establishing asymmetric division. β1 is also important to stem cell maintenance. CD133 is a marker because it is generally found in progenitor stem cells, linking it to a stem cell. CD133+ prostate cells use their stem cell like features developing prostatic-like acini in immunocompromised male mice. CD44 is a cell surface protein involved in cell-to-cell interaction, migration and adhesion. Stem cell antigen 1 is expressed in the tissue of several stem and progenitor stem cells including, cardiac mammary, hematopoietic, testicular, integumentary and muscular. These markers have been found in prostate cancers thus giving credence to this theory (Tu & Lin, 2012). It was also found that cancers that had CD44 were much more tumorigenic and metastatic than cancers without CD44. This further proves that these markers have relevance when it comes to identifying cancers (Patrawala, et al., 2007). These two studies indicate these classic stem cell markers are present in cancers and furthermore they enhance the growth and metastasis of the cancer when they're present.

Breast cancer was also examined for these markers. The researchers analyzed surgically removed breast cancer tissue in 47 cases of only invasive duct carcinoma (IDC), 135 cases of IDC with ductal carcinoma in situ (DCIS), 35 cases of DCIS with microinvasion, 58 cases of pure DCIS and 73 cases of IDCs with adjacent DCIS. Four major subtypes of breast cancer were looked for in this analysis: luminal A, luminal B, HER2+, and basal-like. Each subtype was defined based on certain characters, luminal A (ER+ and/or PR+, HER2–), luminal B (ER+ and/or PR+, HER2+), HER2+ (ER–, PR–, HER2+), basal-like (ER–, PR–, HER2–, basal cytokeratin+, and EGFR+/–). CD44+/CD24– and CD44–/CD24+ cells were found by way of double immunohistochemistry. It was found that luminal A tumors were least common in DCIS with microinvasion, luminal B tumors were least common in IDC alone, and basal-like tumors were least common in pure DCIS groups. CD44, CD24 and ALDH-1 markers were analyzed in normal breast tissue they were then compared to cancerous breast tissue. In normal breast tissue CD44 was localized to the basal, myoepithelial, and a subset of luminal epithelial cells. CD24 was found on the apical membranes of luminal cells while ALDH1 was heterogeneously expressed in luminal and basal cells. CD44 was expressed in 57% of IDC only samples, 59% IDCs with DCIS samples, 62% of DCIS with microinvasion samples, and 85% of DCIS samples. CD24 was not nearly as prevalent as it was present in 24% IDC only tumors, 38% of IDC with DCIS tumors, 59% of DCIS with microinvasion tumors and 62% of DICS tumors. While ALDH1 was not commonlyf ound in any of the four subtypes, it was far more common in IDC alone and IDC with DCIS than the other two subtypes of DCIS with microinvasion and DCIS alone, 9%, 6%, 3%, 3%, respectively (Park, et al., 2010). These figures point to the fact that there is an association between stem cell markers and breast cancer, further legitimizing the stem cell cancer theory.

Head and neck squamous cell carcinoma (HNSCC) such as cancers of the oral cavity, pharynx, larynx, paranasal sinuses, nasal cavity, salivary glands, or head and neck lymph nodes were studied to aid in further proving stem cell theory. Multi-modality therapy including surgery, has been emphasized as the method of treatment, yet the five-year survival rate for HNSCC is 0-40%, with no significant improvements in the past 30 years. A study was done using tissue specimens of cervical lymph nodes, primary tumors, and normal mucosa of patients undergoing surgical treatment of squamous cell carcinomas of multiple sites in the upper aerodigestive tract. A total of 82 primary tumors and 24 metastatic lymph nodes from 82 patients were analyzed. Several variants of CD44 were tested for: CD44s, CD44 v3, CD44 v6, and CD44 v10. It was found that a majority of the cells from both the primary tumors and lymph nodes presented strong expression of all 4 variants. CD44v3, v6 and v10 had a higher proportion of being strongly expressed in lymph nodes than they did in primary tumors. Strong expression of CD44 v3 in primary tumors was also proven to have association with lymph node metastasis. Strong expression of CD44 v10 in primary tumors showed association with radiation failure and with distant metastasis. The expression of CD44 v6 was significantly associated with perineural invasion. Next, an analysis was performed with regard to disease free survival and overall survival. Overall tumor stage was

found to be correlated with shorter disease-free interval. Non-oropharyngeal primary site, positive cervical lymph nodes, distant metastasis, CD44 v6 and CD44 v10 expression, in primary tumors, were all significantly associated with worse disease-free survival. Prior radiation therapy, expression of CD44s and, both the standard and variant form of CD44, in metastatic lymph nodes, were all not significantly associated with disease free interval or overall survival. Expression of CD44s, v3, v6, v10 were all associated with advanced primary tumor stage, treatment failure, reduced disease-free interval, and metastasis (Wang, et al., 2009). These stem cell markers are all indicative of very poor prognosis in HNCSS patients.

Researchers analyzed two cell groups of one patient who suffered from colon cancer, the primary tumor cell (SW480) and the metastatic lymph node (SW620). These cells were analyzed by phase contrast microscopy and were revealed as having two separate morphologies. SW480 was shown to have 80% of its fully adhered cells to be irregularly shaped, while 20% were spindle-like. SW620 displayed a more mixed morphology amongst its cells with 53% of its adhered cells as elongated spindle-shaped and the remaining 47% were either more rounded spindles or irregularly shaped. The two cell lines displayed similar measures of cell growth normal to their respective cell line's. When measuring migratory potential, SW480 cells were found to have a significantly higher migratory potential than SW620 cells. Several stem cell markers were analyzed in each cell line including, CD338, CD44, CD133, CD24 and CD49f. SW620 revealed a 50.6% proportion of CD44+/CD133+ cells and SW480 displayed 28.6%. But the proportion of CD44+/CD133- cells favored SW480 over SW620 with 54.3% and 20.7% respectively. CD44+/CD24- cells were abundant in both cell lines with SW480 having 62.7% and SW620 having 75.3%. The presence of CD49f+/CD338- was the highest with SW480 and SW620 expressing it at 98 and 99%. Because of the prevalence in both groups of cell lines, it was deemed that these stem cell markers were not significant enough to differentiate between SW480 and SW620 in vitro cells (Slater, et al., 2018). While utilizing stem cells did not prove to be a method to differentiate between colon and metastatic tumors, it does prove the presence of these stem cell markers in cancers.

Utilizing the stem cell theory, researchers have developed a new treatment for leukemic stem cells (LSCs) that reside mainly in the bone marrow. Chronic myeloid leukemia (CML) and acute myeloid leukemia (AML) were analyzed. CML is categorized as a clonal hematopoietic stem cell that is caused by a translocation of a fusion of two parts of two separate chromosomes, ALB1 (chromosome 9) and BCR (chromosome 22). AML is the most common form of adult leukemia and is categorized by infiltration of leukemic cells into the bone marrow and blood. The current therapies have an overall survival of roughly 40% in patients under 60 and decline by 5-15% in older patients. AML is very difficult to treat because of how drug resistant the disease is. While CML and AML are both considered to have leukemia stem cells, the environment of the bone marrow that contains many growth factors only expedites the growth process. The markers used to indicate CML LSCs are CD25 IL-1 and CD26 have been suggested as markers that are specific to this disease as opposed to other stem cells. CML LSCs vary from ALM LSC in that CML LSCs are defined as CD34+/CD38- fraction whereas AML LSCs are composed of heterogenous populations and aside from CD34+/CD38- they also are in CD34+/CD38+ and CD34-. The treatment method for these cancers is to disconnect the cancer from the growth promoting bone marrow environment thus making them more sensitive to conventional therapy. There are several compounds being studied as possible ways to disconnect the AML or CML from the bone marrow such as: BL-8040, CAR-LMC, Ruxolitinib, AMD3100, TH-302, Aflibercept, AS101, AMG 386, SRF231, TTI-621, CC90002 Hu5F9-G4, LY3039478. These compounds all have different target cites but are all designed to disconnect the cancer from the growth advances provided by the bone marrow. IL-1RAP has also been shown as a good marker to target CML LSCs in a more selective manor because of its specific expression in CML LSCs. Inducing apoptosis is a common approach to AML treatment (Houshmand, et al., 2019).

Antibodies targeting IL-1RAP were thought as a possible way to treat CML LSCs without harming normal stem cells. The antibodies mAb81.2 and mAb3F8 were used and generated by the hybridoma technique. The cell cultures were bone marrow and peripheral blood from healthy volunteers and CML patients. The CML cells were stimulated with IL-1B, IL-33, IL-36 or SCF. IL-1B and SCF resulted in a slight expansion of CD34- CML progenitor cells. The stimulation as a result IL-1B on CD34+/CD38- cells resulted in a 30-fold increase in cell numbers as opposed to normal cells that responded weakly. In vivo samples were studied to show the therapeutic effects of IL-1RAP antibodies. Mice who expressed IL-1RAP were treated with mAb81.2 which resulted in prolonged survival. The treatment proved to be very effective to the point where the treatment was stopped after 45 days, yet the mice survived an additional 12 days with 2 mice living until day 101. Several of these mice displayed significantly lower bone marrow leukemic cell levels compared with

control mice. These antibodies are effective because they block the signals of IL-1 as well as initiating effector cells to kill tumor cells. This treatment does not affect normal human stem cells because normal stem cells do not express IL1RAP (Agerstam, et al., 2016). This study shows tremendous promise of utilizing the stem cell theory's principles as a route of treatment.

Conclusion

While there is a lot of data supporting each understanding of cancer development, there seems to be one correct approach to cancer; it appears that the correct answer is not one of these three theories rather a combination of the immunological theory and the somatic mutation theory. The immunological theory seems almost entirely correct based on the utilization of CAR-T and CAR-NK, DC-CIK as successful methods of treatment as well as the case-report of a tetanus shot proving to increase cancer prognosis. The issue with solely using the immunological theory is that it better explains the treatment of cancer and what should happen to prevent cancers from developing (NK cells) but it does not address why a cancer cell forms. Rather it only states once a cancer forms the immune system should prevent it from developing. The somatic mutation theory explains why a cancer starts to develop but the immunological theory explains how to prevent it from continual growth. These theories, in tandem, are the best explanation of cancer development.

References

Agerstam, H. et al., 2016. IL1RAP antibodies block IL-1–induced expansion of candidate CML stem cells and mediate cell killing in xenograft models. Blood, 128(23), pp. 2683-2693.

Anon., 2018. Cancer. [Online]
Available at: https://www.who.int/news-room/fact-sheets/detail/cancer
[Accessed 16 October 2019].

Anon., n.d. The Stem Cell Theory of Cancer. [Online]
Available at: https://med.stanford.edu/ludwigcenter/overview/theory.html
[Accessed 23 October 2019].

Duffy, M. J., Synnott, N. C. & Crown, J., 2017. Mutant p53 as a target for cancer treatment. European Journal of Cancer, Volume 83, pp. 258-265.

Graham, C., Hewitson, R., Pagliuca, A. & Benjamin, R., 2018. Cancer immunotherapy with CAR-T cells – behold the future. Royal College of Physicians, 18(4), pp. 324-328.

Haelle, T., 2015. Tetanus Vaccine Boosts Cancer Vaccine In Fighting Brain Tumor. [Online]
Available at: https://www.forbes.com/sites/tarahaelle/2015/03/15/tetanus-vaccine-boosts-cancer-vaccine-in-fighting-brain-tumor/#2c14402a210a
[Accessed 24 November 2019].

Houshmand, M. et al., 2019. Bone marrow microenvironment: The guardian of leukemia stem cells. World J Stem Cells, 11(8), pp. 476-490.

Hu, W. et al., 2019. Cancer Immunotherapy Based on Natural Killer Cells: Current Progress and New Opportunities. Frontiers In Immunology.

Imai, K. et al., 2000. Natural cytotoxic activity of peripheral-blood lymphocytes andcancer incidence: an 11-year follow-up study of a generalpopulation. The Lancet, Volume 356, pp. 1795-1799.

Kuchenbaecker, K. B. et al., 2017. Risks of Breast, Ovarian, and Contralateral Breast Cancer. Jama Network, 317(23), pp. 2402-2416.

Le Gall, C. M., Weiden, J., Eggermont, L. J. & Figdor, C. G., 2018. Dendritic cells in cancer immunotherapy. Nature Materials, Volume 17, pp. 472-477.

Lopez, A. G., Seoane, J. M. & Sanjuan, M. A., 2016. Dynamics of the cell-mediated immune response to tumour growth. The Royal Society Publishing, pp. 1-14.

Miki, Y., Swensen, J., Shattuck-Eidens, D. & Futreal, P. A., 1994. A Strong Candidate for the Breast and Ovarian Cancer Susceptibility Gene BRCA1. Science, Volume 266, pp. 66-71.

Mitchell, D. A. et al., 2015. Tetanus toxoid and CCL3 improve dendritic cell vaccines in mice and glioblastoma patients. Nature, Volume 519, pp. 366-369.

Park, S. Y. et al., 2010. Heterogeneity for stem cell-related markers according to tumor subtype and histologic stage in breast cancer. Clinical Cancer Research, 16(3), pp. 876-887.

Patrawala, L., Calhoun-Davis, T., Schneider-Broussard, R. & Tang, D. G., 2007. Hierarchical Organization of Prostate Cancer Cells in Xenograft Tumors: The CD44+ A2B1+ Cell Population Is Enriched in Tumor-Initiating Cells. Cancer Research, 67(14), pp. 6796-6805.

Shamloo, B. & Usluer, S., 2019. p21 in Cancer Research. Cancers, 11(8), p. 1178.

Siegel, R., Naishadham, D. & Jemal, A., 2013. Cancer statistics, 2013. CA: A Cancer Journal for Clinicians, Volume 63, pp. 11-20.

Singh, B. H. & Gulley, J., 2014. Therapeutic Vaccines as a Promising Treatment Modality Against Prostate Cancer:

Rationale and Recent Advances. Therapeutic Advances in Vaccines and Immunotherapy, 2(5), pp. 137-148.

Slater, C., De La Mare, J.-A. & Edkins, A. L., 2018. In vitro analysis of putative cancer stem cell populations and chemosensitivity in the SW480 and SW620 colon cancer metastasis model. Oncology Letters, 15(6), pp. 8516-8526.

Smid, M. et al., 2006. Genes Associated With Breast Cancer Metastatic to Bone. Journal of Clinical Oncology, 24(15), pp. 2261-2267.

Spaans, V. M. et al., 2015. Precise Classification of Cervical Carcinomas Combined with Somatic Mutation Profiling Contributes to Predicting Disease Outcome. Plos One, 10(7), pp. 1-18.

Takimoto, R. et al., 2002. The Mutant p53-Conformation Modifying Drug, CP-31398, Can Induce Apoptosis. Cancer Biology & Therapy, Volume 1, pp. 47-55.

Tu, S.-M. & Lin, S.-H., 2012. Prostate Cancer Stem Cells. Clinical Genitourinary Cancer, 10(2), pp. 69-76.

Walker, M. G. et al., 1999. Prediction of Gene Function by Genome-Scale Expression Analysis: Prostate Cancer-Associated Genes. Cold Spring Harbor Laboratory Press, Volume 9, pp. 1198-1203.

Wang, S. J. et al., 2009. CD44 variant isoforms in head and neck squamous cell carcinoma progression. Laryngoscope, 119(8), pp. 1518-1530.

Wang, W., Takimoto, R., Rastinejad, F. & El-Diery, W. S., 2003. Stabilization of p53 by CP-31398 Inhibits Ubiquitination without Altering Phosphorylation at Serine 15 or 20 or MDM2 Binding. Molecular and Cellular Biology, 23(6), pp. 2171-2181.

Xie, Y. et al., 2017. Effect of Dendritic cell-cytokine induced killer cells in patients with advanced colorectal cancer combined with first-line treatment. World Journal of Surgical Oncology, 15(209).

Zilfou, J. T. & Lowe, S. W., 2009. Tumor Suppressive Functions of p53. Cold Spring Harbor Perspectives in Biology, pp. 1-13.