Cancer is a Functional Repair Tissue

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Abstract: When a wound occurs, growth and repair genes (GR genes, such as oncogenes, proto-oncogenes, etc.) in surrounding cells are activated and secretion of growth and repair factors (GR factors, such as growth, stem cell, and stimulating factors, etc.) is induced to heal the wound. However, if the wound is persistent due to chronic physical (radiation, electromagnetic field, trauma, particles, etc.), chemical (carcinogens, toxic chemicals, heavy metals etc.) or biological (aging, free radicals, inflammation, nutrient deficiency, bacteria and virus infections, stress, etc.) damage, amplification of GR gene activation in surrounding cells may lead to a clinical cancer. Based on the commonalities between cancer and wound healing, a new hypothesis of cancer is presented: Malignancies are not passive mutated useless masses; rather, they are functional tissues produced by GR gene activation to secrete GR factors in an effort to heal persistent wounds in the body. Based on the hypothesis, current cancer treatments aimed at killing cancer cells only may be misguided. The logical extension of the hypothesis is that cancer treatment focused on wound healing by limiting causes of persistent wounds, providing repair cells, GR factors, and substrates required by repair cells may yield more fruitful results than treatments focused on killing cancer cells alone. Spontaneous regressions of cancer, although rare, may be successful examples of serendipitous spontaneous wound healing. Standard therapies aimed at killing cancer cells, should be limited to adjuvant status for limiting symptoms or buying time for completion of the wound healing process. Attempts to destroy cancer cells without healing underlying persistent wounds will allow for eventual recurrence.

BACKGROUND

Current theories hold that cancers are abnormal tissues triggered by gene mutations. Standard cancer treatments are primary removal via surgery and/or attempts to destroy tumor tissue using radiation and/or chemotherapy. In spite of improvements in earlier detection and diagnosis, current treatments have not radically improved survival. From 1950 to 1995, five year survival rates for several malignant tumor types (pancreas, liver, stomach, lung, brain and esophagus) have increased only between 3% and 9%[1].

Proto-oncogenes and oncogenes are expressed not only in cancer[2], but also in pregnancy[3], embryonic development[4,5], wound healing[6] and growth factor synthesis[7]; indicating the products of these genes are involved in normal, non-malignant, growth and repair processes.

Many cancer risk factors are associated with wound-like conditions. For example: smoking causes chronic inflammation of the lungs and is a risk factor for lung cancer[8]; inflammation of the liver, colon and prostate increase the risk of cancer developing in those tissues[9]; cervical erosion is a risk factor for cervical cancer[10]; and ulcers are risk factors for gastric cancer[11], etc.

Oncogenes have broad antiapoptotic functions[12,13] which is a cellular feature found in wound healing. Similarities between oncogene expression and antiapoptosis activity in normal physiological processes (wound healing, development, and pregnancy) and malignancies reveal relationships between mechanisms of carcinogenesis and the evolution of mammalian repair.

HYPOTHESIS

Wound healing

During growth or reproduction phases, growth and repair genes (GR genes, all tissue growth and repair genes, such as oncogenes, proto-oncogenes, etc.) are activated to reproduce cells so tissues can

develop[3,14,15]. When a wound occurs, the healing process begins: platelets seal broken capillaries; T cells, macrophages and NK cells migrate into the tissue to remove debris and dead cells[16]; leaked platelets, T cells, monocytes and macrophages secrete growth and repair factors[17-19] (GR factors, all tissue growth and repair promoting substances, such as growth factors, stem cell factors, some cytokines, growth and repair related hormones, etc). GR genes in surrounding cells are activated and secrete more GR factors[20]. GR factors recruit stem cells from neighboring tissues and the bone marrow to the wound site[21]. Stem cells differentiate into various tissues under growth factor[22] influence and finally repair the wound in concert with other cells. When repair is complete, the GR genes are turned off (or tumor suppressor genes are turned on[23]) and homeostasis is restored.

Cancer as a functional tissue

However, if the wound is persistent due to chronic physical (radiation, electromagnetic field, trauma, particles, etc.), chemical (carcinogens, toxic chemicals, heavy metals etc.) or biological (aging, free radicals, inflammation, nutrient deficiency, bacteria and virus infections, stress, etc.) damage, local and neighboring stem cells may become exhausted[24,25]. Migration and replication of stem cells from bone marrow may be insufficient to heal the wound if local stresses remain, particularly in an aging individual whose stem cells have decreased reparative capacity. It is known that the expansion potential of hemotopoietic progenitor cells is lower in cancer patients than in controls[26]. As the wound persists, more and more GR genes activated in surrounding cells induce malignant transformation that can lead to clinical cancer[27].

Malignant transformation of cells at the wound site allows for increased secretion of a wider variety of GR factors[28-31] in an attempt to heal the wound by recruitment and stimulation of stem cells from other sites[24,32,33]. Therefore, malignancies may not be passive mutated masses. Rather, they are functional tissues produced by GR gene activation to secrete GR factors in an effort to heal persistent wounds.

Evidence to support the notion that malignant cells may be a “last ditch” effort to heal a chronic wound can be demonstrated by the fact that tumor cells secrete functional repair molecules, many of which are produced during wound healing[34,35]. Growth factors and stem cell factors are highly expressed in cancer tissue[31] and can be found in relatively high concentrations in the sera of cancer patients[36]. Given the hypothesis, cancer cells would disappear through differentiation and apoptosis at the completion of wound healing, and no clinical cancer would emerge. The fact that pathologic cancers are found during autopsy at a higher incidence than clinical cancer[37,38] suggests that some wounds might be healed by sub clinical cancer.

Location

In the context of the hypothesis, malignancies would most likely arise in tissues that most frequently activate GR genes, and tissues with the highest propensity for non-healing wounds. Tissues with frequent repair gene activation are those with rapid turnover or frequent repair needs, such as bone and blood during growth development, reproductive system related tissues during pregnancy, digestive mucosa, respiratory and urinary endothelium, skin, etc. Frequent repair gene activation subsequent to higher metabolic and cell division rates in these tissues increases the risk of malignant transformation. This may explain higher incidence rates of bone cancer and leukemia in young people during bone development[39,40], increased rates of reproductive malignancy during pregnancy[41] and overall higher cancer incidence in high cell turnover tissues such as found in the digestive, respiratory, genital, and urinary systems[42].

POTENTIAL THERAPIES BASED ON HYPOTHESIS:

Traditional cancer treatments, including surgery, radiation and chemotherapy aim to eliminate cancer masses. However, malignant tissue produces vital factors for repair of non-healing wounds. Therefore, traditional cancer treatments may actually be working against an organism's attempts to heal. Traditional treatments do not provide GR factors and necessary substrates to damaged tissues. Instead they remove the GR factor factory (malignant cells). In the case of surgical cure of malignancy, it is likely that the non-healing wound is removed along with the malignancy, and the GR factors are no longer required. The tumor micro-environment is likely worsened by tumor reduction via chemotherapy or radiation. The damage to normal tissue by chemotherapy and radiation may well induce more malignant formation to overcome the damage of the treatment.

Based on the hypothesis, cancer treatment strategies should be comprised of three facets: (1) removal of known physical, chemical, or biological causes of persistent wounds; (2) provision of a critical mass of repair cells to the site of malignancy; and (3) delivery of a critical mass of GR factors and substrates required for wound healing to the site of malignancy. When the wound is healed, cancer cells will eventually disappear through differentiation or apoptosis. Spontaneous remissions of cancer[43-45], although rare, may be successful examples of serendipitous spontaneous wound healing. Standard therapies aimed at killing cancer cells, should be limited to adjuvant status for limiting symptoms or buying time for completion of the wound healing process. Attempts to destroy cancer cells without healing underlying persistent wounds will allow for eventual recurrence.

Repair cells

Supplying enough repair cells to wound sites for a sufficient amount of time to elicit termination of wound healing is one of three cornerstones of successful cancer therapy based on the hypothesis. Stem cells are the most likely candidates for repair cells. Stem cells are known to home in on, and repair, damaged tissue. Both autologous and allogeneic stem cells can be recruited into the wound site for the wound healing[21,24]. Some immune stimulants that showed anticancer effect are found to be stem cell stimulants also, such as glucans[46,47]. Stem cell stimulators alone have demonstrated benefit to cancer patients, ie granulocyte-macrophage colony stimulating factor[48,49]. Placental extracts, a source of stem cell growth factors[50,51] may be responsible for the responses of various cancers to treatment with placenta extracts[52]. Placental stem cells naturally transplanted into the mother during normal pregnancy can remain in maternal marrow and tissue throughout life[53]. This phenomenon may contribute to the phenomenon of women having a lower cancer incidence than men after 50 years of age[42].

GR factors and substrates

Supplying GR factors and repair cell substrates to wound sites for a sufficient amount of time to elicit termination of wound healing is the second cornerstone of treatment based on the hypothesis. Wound healing is a series of complex physicochemical interactions that require various micronutrients at every step[35]. A multitude of vitamins, minerals, amino acids, fatty acids, glycosaminoglycans, growth factors and oxygen are necessary for optimal wound healing[35,54-59]. Hormones, vitamins, growth factors, and cytokines are being added to conventional cancer therapies (chemo-, surgical, and radiation therapy) and recently became the "fourth arm" of cancer treatment[60]. The conflicting results of effects of nutrition in cancer treatment[60-62] may be due to incomplete nutrient supplementation and/or lack of adequate numbers of repair cells. For example, one study found that vitamin C treatment of patients with a variety of cancer resulted in 10% excellent responders versus 40% in patients treated with Vitamin C plus other nutrients[63]. If supplemented substrates are not adequate to overcome localized deficiencies at the wound site, completion of wound healing is unlikely[64]. Clinical cancer often accompanies substrate deficiencies[65]. These substrate deficiencies affect cell replication and stem cell activities (proliferation, differentiation, responses to growth hormone and growth factors, etc)[66]. Therefore, even if repair cells (such as stem

cells) exist in adequate numbers at the wound site, substrate deficiency would lead to incomplete wound healing. Because deficiencies of individual nutrients at the wound site are not generally measurable, provision of a complete battery of GR factors and substrates to cover any potential deficiency is desirable. This complete battery of GR factors and substrates that are necessary for cell metabolism normally, can be called whole cellular nutrients (WCN) including growth factors, stem cell factors, some cytokines, growth and repair related hormones, vitamins, minerals, nucleic acids, amino acids, fatty acids, glycosaminoglycans, carbohydrates, antioxidants, oxygen, etc. The risk, if WCN is supplied in known non-toxic concentrations, is minimal to none.

CONCLUSION

According to the hypothesis presented, malignancies may develop via activation of GR genes as a repair mechanism to promote completion of healing of persistent wounds. The hypothesis suggests three key elements for effective cancer treatment: (1) removal of known physical, chemical, or biological causes of persistent wounds (2) delivery of a critical mass of reparative cells to the site of malignancy; and, (3) delivery of WCN required for wound healing to the site of malignancy.

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References:

1. H. Gilbert Welch et al: Are Increasing 5-Year Repair Rates Evidence of Success Against Cancer? JAMA. 2000;283:2975-2978.
2. MW Anderson et al: Role of proto-oncogene activation in carcinogenesis. Environ Health Perspect, November 1, 1992; 98: 13-24.
3. H Meden et al: Elevated serum levels of a c-erbB-2 oncogene product in ovarian cancer patients and in pregnancy. J Cancer Res Clin Oncol, January 1, 1994; 120(6): 378-81.
4. T Attie-Bitach et al: Expression of the RET proto-oncogene in human embryos. Am J Med Genet, Dec 1998; 80(5): 481-6.
5. S.M. Quenby et al: Oncogenes and tumour suppressor genes in first trimester human fetal gonadal development. Mol. Hum. Reprod., Aug 1999; 5: 737 - 741.
6. Y Okada et al: Expression of fos family and jun family proto-oncogenes during corneal epithelial wound healing. Curr Eye Res, Aug 1996; 15(8): 824-32.
7. Stiles, CD: The biological role of oncogenes--insights from platelet-derived growth factor: Rhoads Memorial Award lecture. Cancer Res., Nov 1985; 45: 5215 - 5218.
8. Emerich S et al: Induction of preneoplastic lung lesions in guinea pigs by cigarette smoke inhalation and their exacerbation by high dietary levels of vitamins C and E. Carcinogenesis, Mar 2005; 26: 605 - 612.
9. EA Platz et al: Epidemiology of inflammation and prostate cancer. J Urol, Feb 2004; 171(2 Pt 2): S36-40.
10. NS Murthy et al: Risk factors for pre-cancerous lesions of the cervix. Eur J Cancer Prev, Feb 2000; 9(1): 5-14.
11. RM Molloy et al: Relation between gastric cancer and previous peptic ulcer disease. Gut, Feb 1997; 40: 247 - 252.
12. H Friess et al: bax, but not bcl-2, influences the prognosis of human pancreatic cancer. Gut, Sep 1998; 43: 414 - 421.
13. Hirotaka Kazama et al: Oncogenic K-Ras and Basic Fibroblast Growth Factor Prevent Fas-mediated Apoptosis in Fibroblasts through Activation of Mitogen-activated Protein Kinase. J. Cell Biol., Feb 2000; 148: 557 - 566.
14. JF Caubet et al: Expression of the c-fos proto-oncogene in bone, cartilage and tooth forming tissues during mouse development. Biol Cell, January 1, 1988; 64(1): 101-4.
15. D Carrasco et al: Developmental expression of the mouse c-rel proto-oncogene in hematopoietic organs. Development, Oct 1994; 120: 2991 - 3004.
16. AD Agaiby et al: Immuno-inflammatory cell dynamics during cutaneous wound healing. J Anat, November 1, 1999; 195 (Pt 4): 531-42.
17. S Blotnick et al: T Lymphocytes Synthesize and Export Heparin-Binding Epidermal Growth Factor-Like Growth Factor and Basic Fibroblast Growth Factor, Mitogens for Vascular Cells and Fibroblasts: Differential Production and Release by $CD4^+$ and $CD8^+$ T Cells. PNAS, Apr 1994; 91: 2890 - 2894.

18. G. Workalemahu et al: Human γδ-T Lymphocytes Express and Synthesize Connective Tissue Growth Factor: Effect of IL-15 and TGF-ß1 and Comparison with αß-T Lymphocytes. J. Immunol., Jan 2003; 170: 153 - 157.
19. G Soslau et al: Cytokine mRNA expression in human platelets and a megakaryocytic cell line and cytokine modulation of platelet function. Cytokine**,** June 1, 1997; 9(6): 405-11.
20. Y Okada et al: Expression of fos family and jun family proto-oncogenes during corneal epithelial wound healing. Curr Eye Res, August 1, 1996; 15(8): 824-32.
21. Y. Son et al: Identification of substance–p as an early inductive cytokine of corneal wound and its possible role in the mobilization of mesenchymal stem cell and corneal wound healing. Invest. Ophthalmol. Vis. Sci., May 2004; 45: 1423.
22. N Lavon et al: Differentiation and isolation of hepatic-like cells from human embryonic stem cells. Differentiation**,** June 1, 2004; 72(5): 230-8.
23. BH Noszczyk et al: p63 expression during normal cutaneous wound healing in humans. Plast Reconstr Surg, October 1, 2001; 108(5): 1242-7; discussion 1248-50.
24. JeanMarie Houghton et al: Gastric Cancer Originating from Bone Marrow-Derived Cells. Science, Nov 2004; 306: 1568 - 1571.
25. B.J. Shin et al: A Case of Limbal Stem Cell Deficiency in a Patient with Chronic Mucocutaneous Candiddiasis Invest. Ophthalmol. Vis. Sci., May 2003; 44: 1359.
26. Guadalupe Martínez-Jaramillo et al: In vitro proliferation and expansion of hematopoietic progenitors present in mobilized peripheral blood from normal subjects and cancer patients. Stem cells and development 13:382–389 (2004).
27. N Ouahes et al: Expression of c-fos and c-Ha-ras proto-oncogenes is induced in human chronic wounds. Dermatol Surg, December 1, 1998; 24(12): 1354-7; discussion 1358.
28. R Dahiya et al: Differential gene expression of transforming growth factors alpha and beta, epidermal growth factor, keratinocyte growth factor, and their receptors in fetal and adult human prostatic tissues and cancer cell lines. Urology, Dec 1996; 48(6): 963-70.
29. S Huang et al: Proliferation of human colon cancer cells: role of epidermal growth factor and transforming growth factor alpha. Int J Cancer, December 2, 1992; 52(6): 978-86.
30. K Mizuno et al: Autonomous expressions of cytokine genes by human lung cancer cells and their paracrine regulation. Jpn J Cancer Res, Feb 1994; 85(2): 179-86.
31. AM Turner et al: Nonhematopoietic tumor cell lines express stem cell factor and display c-kit receptors. Blood, Jul 1992; 80: 374 - 381.
32. FM Cicuttini et al: The effect of recombinant stem cell factor (SCF) on purified CD34-positive human umbilical cord blood progenitor cells. Growth Factors, January 1, 1992; 6(1): 31-9.
33. Huanxiang Zhang et al: VEGF is a chemoattractant for FGF-2–stimulated neural progenitors. J. Cell Biol., Dec 2003; 163: 1375 - 1384.
34. JP Lefaucheur et al: Angiogenic and inflammatory responses following skeletal muscle injury are altered by immune neutralization of endogenous basic fibroblast growth factor, insulin-like growth factor-1 and transforming growth factor-beta 1. J Neuroimmunol, October 1, 1996; 70(1): 37-44.
35. NA Meyer et al: Nutrient support of the healing wound. New Horiz, May 1, 1994; 2(2): 202-14.
36. B Mroczko et al: Stem cell factor and macrophage-colony stimulating factor in patients with pancreatic cancer. Clin Chem Lab Med, March 1, 2004; 42(3): 256-60.
37. H. Gilbert Welch et al: Using Autopsy Series To Estimate the Disease "Reservoir" for Ductal Carcinoma in Situ of the Breast: How Much More Breast Cancer Can We Find? Ann Intern Med, Dec 1997; 127: 1023 - 1028.
38. GN Stemmermann et al: Unsuspected cancer in elderly Hawaiian Japanese: an autopsy study. Hum Pathol, November 1, 1982; 13(11): 1039-44.
39. HD Dorfman et al: Bone cancers. Cancer, January 1, 1995; 75(1 Suppl): 203-10.
40. C Yang et al: Incidence survey of leukemia in China. Chin Med Sci J, June 1, 1991; 6(2): 65-70.
41. JF Haas: Pregnancy in association with a newly diagnosed cancer: a population-based epidemiologic assessment. Int J Cancer, Aug 1984; 34(2): 229-35.
42. United States Cancer Statistics: 2000 Incidence and Mortality Web-based Report. http://apps.nccd.cdc.gov/uscs/index.asp?Year=2000
43. Carrie Printz: Spontaneous Regression of Melanoma May Offer Insight Into Cancer Immunology. J Natl Cancer Inst, Jul 2001; 93: 1047 - 1048.
44. Papac RJ: Spontaneous regression of cancer: possible mechanisms. In Vivo. 1998 Nov-Dec;12(6):571-8.
45. Max Gerson: The cure of advanced cancer by diet therapy: A summary of 30 years of clinical experimentation. Physiol.chem. & Physics 10 (1978): 449-464.
46. ML Patchen et al: Effects of pre- and post-irradiation glucan treatment on pluripotent stem cells, granulocyte, macrophage and erythroid progenitor cells, and hemopoietic stromal cells. Experientia, November 15, 1984; 40(11): 1240-4.
47. PM Kidd: The use of mushroom glucans and proteoglycans in cancer treatment. Altern Med Rev, February 1, 2000; 5(1): 4-27.

48. SK Sohn et al: GM-CSF-based mobilization effect in normal healthy donors for allogeneic peripheral blood stem cell transplantation. Bone Marrow Transplant, July 1, 2002; 30(2): 81-6.
49. JA Neidhart: Dose-intensive treatment of breast cancer supported by granulocyte-macrophage colony-stimulating factor (GM-CSF). Breast Cancer Res Treat, December 1, 1991; 20 Suppl: S15-23.
50. DE Seubert et al: A study of the relationship between placenta growth factor and gestational age, parturition, rupture of membranes, and intrauterine infection. Am J Obstet Gynecol, June 1, 2000; 182(6): 1633-7.
51. F Bissonnette et al: Transforming growth factor-alpha and epidermal growth factor messenger ribonucleic acid and protein levels in human placentas from early, mid, and late gestation. Am J Obstet Gynecol, January 1, 1992; 166(1 Pt 1): 192-9.
52. Govallo, V: Immunology of pregnancy and cancer. Nova Science Publishers, Inc.; 1993
53. K O'Donoghue et al: Microchimerism in female bone marrow and bone decades after fetal mesenchymal stem-cell trafficking in pregnancy. Lancet, July 10, 2004; 364(9429): 179-82.
54. D MacKay et al: Nutritional support for wound healing. Altern Med Rev, November 1, 2003; 8(4): 359-77.
55. RL Ruberg et al: Role of nutrition in wound healing. Surg Clin North Am, August 1, 1984; 64(4): 705-14.
56. S. Noguchi et al: Effect of salivary epidermal growth factor on wound healing of tongue in mice. Am J Physiol Endocrinol Metab, Apr 1991; 260: 620 - 625.
57. MA Mooney et al: Evaluation of the effects of omega-3 fatty acid-containing diets on the inflammatory stage of wound healing in dogs. Am J Vet Res, July 1, 1998; 59(7): 859-63.
58. DH McDaniel et al: Accelerated laser resurfacing wound healing using a triad of topical antioxidants. Dermatol Surg, June 1, 1998; 24(6): 661-4.
59. Chandan K. Sen et al: Oxygen, Oxidants, and Antioxidants in Wound Healing: An Emerging Paradigm. Ann. N.Y. Acad. Sci., May 2002; 957: 239 - 249.
60. AP Lupulescu et al: Hormones, vitamins, and growth factors in cancer treatment and prevention. A critical appraisal. Cancer, Dec 1996; 78(11): 2264-80.
61. Keith I et al: Vitamin C in Alternative Cancer Treatment: Historical Background. Integr Cancer Ther, Jun 2003; 2: 147 - 154.
62. Eric J et al: Vitamin C and Vitamin E Supplement Use and Colorectal Cancer Mortality in a Large American Cancer Society Cohort. Cancer Epidemiol. Biomarkers Prev., Jan 2001; 10: 17 - 23.
63. Hoffer A et al: Hardin Jones biostatistical analysis of mortality data for a second set of cohorts of cancer patients with a large fraction surviving at the termination of the study and a comparison of repair times of cancer patients receiving large regular oral doses of vitamin C and other nutrients with similar patients not receiving these doses. J of Orthomolecular Medicine, 8:157-167, 1993.
64. TM Reynolds: The future of nutrition and wound healing. J Tissue Viability, January 1, 2001; 11(1): 5-13.
65. TD Doerr et al: Effects of zinc and nutritional status on clinical outcomes in head and neck cancer. Nutrition, June 1, 1998; 14(6): 489-95.
66. RO Oreffo et al: Maternal protein deficiency affects mesenchymal stem cell activity in the developing offspring. Bone, July 1, 2003; 33(1): 100-7.