Personalized and tailored cancer treatment

The cancer protein “fingerprint” concept

How to turn cancer into a silent and chronic disease

(Theoretical paper)

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Cancer causes many deaths per year worldwide. Despite some progress in studying the origin of it, has not yet managed to find a way to cure it. For this reason I intend, at least, that patients suffering from cancer do not die and have a chance to survive while waiting for a cure.

This theory is based on the fact that all human tumors produce substances, most of the times proteins, which runs free in the blood. Therefore, it could be detected with a blood test searching for this anomalous protein through a proteinogram or some kind of protein analysis.

Once this protein is detected, it is necessary to tailor specific monoclonal antibodies against this tumor protein (against the cell surface or occasionally, intracellular), and which is running in the blood.

One of the advantages of this method is that these proteins belong only to the tumor. They are not present in another disease or in healthy humans. They are specific to the tumor.

These antibodies would neutralize the protein and would attack the tumor cells specifically, because this protein or substance usually shows itself on the cell surface or come from inside the cancer cell. If this substance were inside the cell, it would be necessary to introduce these antibodies into the cell or to design the necessary strategies to achieve this aim, for example by liposomes or another device to carry inside the cell the substance.

Another important issue to consider is that once the substance (protein) is identified, and the monoclonal antibodies are produced, these antibodies could be attached to fluorescent elements (fluorophore-labeled antibodies or tagging specific oncomolecules with

fluorescent labels[1]), converting the tumor cells in fluorescently labeled cells, and could detect them by whole-body bioluminescence imaging, trying to ascertain if these protein/cells correspond to the tumor and to avoid cross reactions with other tissues or cells.

In this way trying to test a specific cancer circulating protein, we can see for instance that CD133, which is a glycosilated protein of cell surface from colon cancer, also it had detected in another cancer types. This protein would express only in cancer stem cells.[2] [3] [4] This concept about cancer stem cells has interesting implications, so from medical as surgical point of view. If we will have success with this kind of therapeutics, I mean, attack specifically cancer stem cells which produce only cancer cells lines, then we would not have the need to do any kind of surgical treatment, because just identifying the stem cells capable of creating cancer and grow up it, it would give us the chance to destroy it selectively without the need to smash the tumor or remove it totally.

The development of inhibitors targeted to proteins encoded by mutated cancer genes has now been achieved with repeated success. The paradigm is best exemplified by imatinib (Gleevec), a potent inhibitor of the Abelson (ABL) kinase, in chronic myeloid leukemia (CML).[5]

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[1] Bates M. A new approach to fluorescence microscopy. Science 3 December 2010;330:1334-1335.

[2] Yeung TM, Mortensen NJ. Colorectal cáncer stem cells. DCR 2009;52:1788-96.

[3] Clarke MF, Dick JE, Dirks PB, *et al*. Cancer stem cells—perspectives on current status and future directions: AACR Workshop on Cancer Stem Cells. Cancer Res 2006;66:9339–44.

[4] Ricci-Vitiani L, Lombardi D, Pilozzi E, *et al*. Identification and expansion of human colon-cancer-initiating cells. Nature 2007;445:111–5.

[5] Druker BJ, Guilhot F, O'Brien SG, et al. Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. N Engl J Med 2006;355:2408-17.

Some studies and investigators had catched the idea in similar way, relating this process with the immune system.[6] One of them was Olivera Finn who discovered the first tumor antigen capable of arousing an immune response.[7] If the cancer generates an immune response, thus it could detect specific antibodies in blood for each tumor, as some authors suggested in other diseases with their respective biomarkers.[8]

Similar lines of investigation had walked with the advent of trastuzumab, monoclonal antibody, for the treatment of breast cancer, in women with positive HER2 cellular receptors. It means the drug blocked these receptors which were in relation with the cancer growth. In the same way, for colon cancer, it was approved cetuximab, an antibody for the EGFR receptor (similar to HER2), and in relation with the normal Kras oncogen.[9] Ergo, in patients with Kras mutated, they would develop resistance to cetuximab.

In another way, may be as another consequence of this theory, exist the antilatency therapy, which came from the HIV infection research. Richman *et al* review one such option: eradication of HIV infection by antilatency therapies.[10] He and other investigators are following the way like us, that the changes in the cell, the cytoplasm or nucleus, could be detected in the blood and the surface of the cells. This issue traduces the situation that the proteins expressed in the cell surface of the tumoral cells were the fingerprints of the tumors, so they would be exclusive of each type of tumor and they don't appear in the

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[6] Bargou et al. Tumor regression in cancer patients by very low doses of a T cell-engaging antibody. Science 15 august 2008;321:974-77.

[7] Leslie M. Directing a life in Science. Science 15 august 2008;321:906-7.

[8] Reddy MM et al. Identification of Candidate IgG Biomarkers for Alzheimer's Disease via Combinatorial Library Screening. Cell, Volume 144, Issue 1, 132-142, 7 January 2011

[9] Kaiser J. Looking for a target on every tumor. Science 2009 October;326:218-20.

[10] Richman DD et al. The challenge of finding a cure for HIV infection. Science 6 March 2009; 323:1304-07.

normal cells. Steenbergen et al[11] published in 1995 their study about HPV virus integrated into the cell of tumor from head and neck and they expressed these oncoproteins. Some investigators has called this phenomenon "genetic signature" [12] referring that each tumor of each patient has an unique way to genetic expression, as a written signature or a fingerprint.[13]

An article published in Science, in relation of this hypothesis of individualized cancer cells and possible therapeutic target, says[14]:

> "In recent work, Langer's teamincorporated the anticancer compound docetaxel into the PLGA polymer matrix and added a targeting molecule that seeks out prostate-specific membrane antigen, a protein expressed on the surface of prostate cancer cells and other types of solid tumor cells. According to Bind's CEO Scott Minick, animal trials showed that the combination of the targeting compound and slow release of the docetaxel by degrading nanoparticles increases the tumor cell concentration of the anticancer drug 20-fold over docetaxel pack-aged in conventional liposomes."

We also read the articles of Langer.[15] [16] [17]

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[11] Steenbergen RD, Hermsen MA, Walboomers JM, Joenje H, Arwert F, Meijer CJ, Snijders PJ. Integrated human papillomavirus type 16 and loss of heterozygosity at 11q22 and 18q21 in an oral carcinoma and its derivative cell line. Cancer Res. 1995 Nov 15;55(22):5465-71.

[12] Nevins JR, Huang ES, Dressman H, Pittman J, Huang AT, West M. Towards integrated clinico-genomic models for personalized medicine: combining gene expression signatures and clinical factors in breast cancer outcomes prediction. Hum Mol Genet 2003;12:R153-R157.

[13] Potti A, Schilsky RL, Nevins JR. Refocusing the War on Cancer: The Critical Role of Personalized Treatment. Scie Transl Med 21 April 2010; Volume 2 Issue 28 28cm13

[14] Robert F. Nanoparticle trojan horses gallop from the lab into the clinic. Science 2010; (330)15th October:314-15.

In the same view of arguments, another biomarker which promises in similar ways as above, it means a cancer fingerprint, is the RNA.[18]

Obviously, the previous theory should be studied and tested in places of great volume of basic and applied research. Meanwhile the investigators could find a definitive treatment for cancer and people would not die because of this disease.

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[15] Farokhzad OC, Cheng J, Teply BA, Sherifi I, Jon S, Kantoff PW, Richie JP, Langer R. Targeted nanoparticle-aptamer bioconjugates for cancer chemotherapy in vivo. Proc Natl Acad Sci U S A. 2006 Apr 8;103(16):6315-20.

[16] Kolishetti N, Dhar S, Valencia PM, Lin LQ, Karnik R, Lippard SJ, Langer R, Farokhzad OC. Engineering of self-assembled nanoparticle platform for precisely controlled combination drug therapy. Proc Natl Acad Sci U S A. 2010 Oct 19;107(42):17939-44. Epub 2010 Oct 4.

[17] Wang AZ, et al ChemoRad nanoparticles: a novel multifunctional nanoparticle platform for targeted delivery of concurrent chemoradiation Nanomedicine (Lond). 2010 Apr;5(3):361-8.

[18] http://news.sciencemag.org/sciencenow/2011/01/a-universal-marker-for-tumor-cel.html