Title: Solving the puzzle about Bowhead whale longevity and its low risk to cancer

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Abstract:

Bowhead whale is the longest living organism and have enormous body size, body mass. According hypothesis, their cells have to proliferate plenty times, in the long run this organism should have high risk to cancer, but it is surprisingly vise versa. There is should be regulation involved in Bowhead whale, which is contributes to repress cancer in their body.

Deep diving of the whale in bottom of ocean, induces hypoxia in the organism. Remarkably, in tumor same condition occurs, and in the human body they succeed to induce angiogenesis, in outcome formed vessels supply cancer cell, which will further grow and increase migratory and metastasis. This paper suggest that Bowhead whale angiogenesis process that manage hypoxia condition in whale body may play important role in repressing cancer. Moreover, paper includes current anti-angiogenesis drugs in clinical approaches, and tries to find solution to their side effects.

Introduction:

One of the longest – living animals of the earth is the Bowhead whale (Balaena mysticetus), which is estimated to live over 200 years. These animals can weigh from 75 to 100 tons, and live entirely in Arctic and sub-Arctic waters. [1]

Before there was assumption about that, if body size and mass big, the greater chance to get mutations in the cell and high risk to the cancer, due to large number of cell replication in the body. Although, the bowhead whale lives more than 200 years and have huge body size, hardly ever gets cancer. Thereby they should maintain protective molecular adaptations relevant to age-related diseases, particularly cancer. [2]

In 2015, Michael Keane, Jeremy Semeiks and several scientists together published a paper in Cell Press Reports about mapping the bowhead whale genome, with the title "Insights into the Evolution of Longevity from the Bowhead Whale Genome", where they reported the sequencing and comparative analysis of the bowhead whale genomes. In paper, scientists after sequencing, identified positive selected genes and bowhead-specific mutations, and tried to correlate them with aging and cancer. Especially, in that paper more focus were given to DNA repair, cancer, cell –cycle linked gene's modifications. Moreover, researchers made an available online data on the website (http://www.bowhead-whale.org) for other interested ones to conduct research further within their information.

My research facilitated from this scientific article, with the aid from their whale genome portal. Close look to the condition and structure of the Bowhead whale might give rewarding solutions to the current issues, related to diseases, against cancers or aging. To be specific, my current focus is on the behavior of the cancer and linking it to the Bowhead whale metabolism, and find how whale able to manage the same condition.

The problem:

The most abundant baleen Minke whale is the closest relative to the Bowhead whale, which diverged from each other only 25-30 million years ago. [3] The catching thing here is that, even though they have around 96% matched protein coding sequences, their characteristic features highly remarkable.

	Lifespan	Body mass
Minke Whale	max. 50 years [4]	<10tons
Bowhead Whale	more than 200 years	70~90tons

The main current issue is how with that small proportion difference in protein coding could lead to significant changes in the phenotype of the two animals. In addition, through this paper I will suggest hypothesis about how bowhead whale could confer cancer resistance.

My idea:

It is highly accepted that during the tumor, cancer cells deprives from oxygen supply, due to active proliferation level of the cells. So, in tumor regions oxygen concentration level significantly lower than in healthy tissues. This condition called tumor hypoxia, and cancer cells alter metabolism in order to support their growth, replication. Furthermore, due to hypoxia tumor cells change their behavior, like extracellular matrix remodeling and increased migratory and

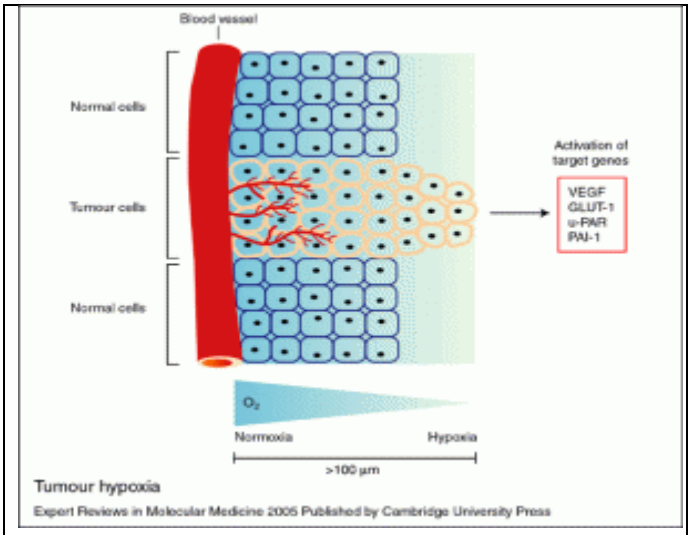

Figure 1. Tumor hypoxia [6]

metastatic behavior. [5] The mechanism that cancer cells turn on during the hypoxia condition is that they release their target genes in angiogenesis, such a vascular endothelial growth factor (VEGF), as a result the new blood vessel formation will happen, which encourages above described tumor behavior.

So far, for whales in order survive had to adapt to deep sights of the oceans, consequently by evolution they induces hypoxia during the prolonged diving under the water. My main idea is that since in Bowhead whale body most of the time observed the hypoxia condition, they somehow can control their angiogenesis. It means they have their distinctive way or metabolism, that make their organism resistant to cancer. Close investigation in this area will unveil an anti- cancer metabolism‘s secret, which in further might be applied to cancer treatment approaches.

There are required close look to the every single gene variants, since almost all protein coding genes almost same with a minke whale. In paper, introduced above, scientists tried to look to ever bowhead-specific amino acid replacement mechanisms in DNA repair, or cell-cycle proteins. However, I wish to investigate Bowhead specific amino acid changes in proteins responsible to angiogenesis process.

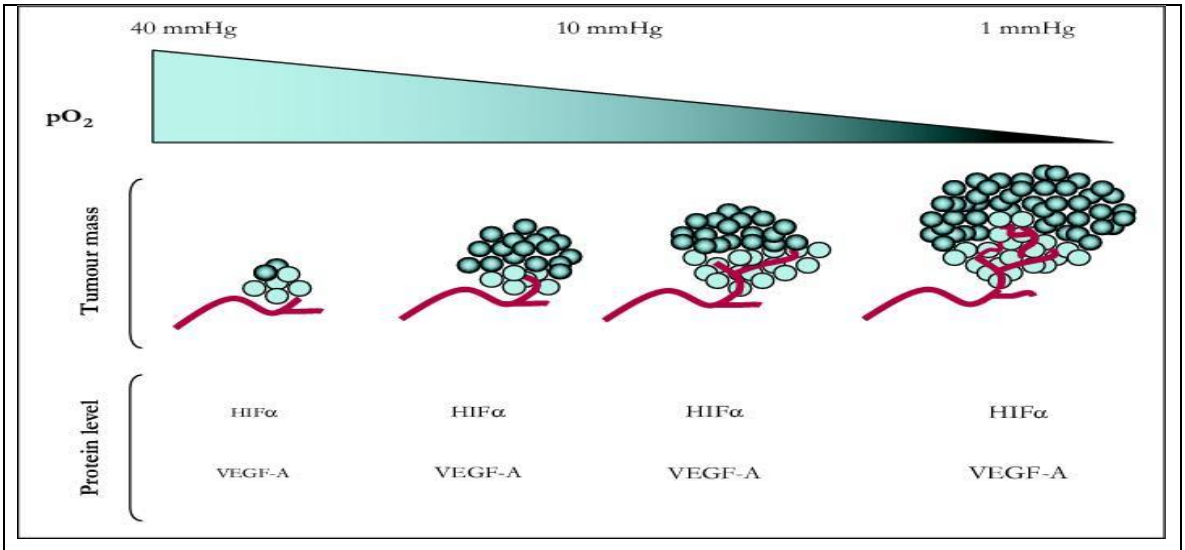

Figure 2. Tumor cells under hypoxic stress (low oxygen partial pressure, PO2) secrete vascular endothelial growth factor-A (VEGF-A) in response to the HIFa.[7]

The details:

Cells undergo a variety of biological responses when placed in hypoxic conditions, including activation of signaling pathways that regulate proliferation, angiogenesis and death. Cancer cells have adapted these pathways, allowing tumors to survive and even grow under hypoxic conditions, and tumor hypoxia is associated with poor prognosis and resistance to radiation therapy. Many elements of the hypoxia-response pathway are therefore good candidates for therapeutic targeting (Harris, 2002).[8]

Furthermore, using Bowhead Whale Genome Portal conducted corresponding analysis for proteins responsible for angiogenesis. Especially, I looked for VEGF co-regulated chemokine 1 (CXCL17) [9], according to data this protein matched with cow protein, and human. Uncommon was that there were no matching information about this protein in between bowhead and minke whale, even though almost all other proteins have been matched. Does that mean that minke whale does not express such protein in their body?

Below in table, matching information between bowhead whale and cow VEGF.

Gene Details

VEGF co-regulated chemokine 1

***Gene match** (Ensembl Protein ID: ENSBTAP00000024820, Cow)*

Protein Percentage	77.12%
cDNA percentage	87.01%
Ka/Ks Ratio	0.71929 (Ka = 0.1327, Ks = 0.1844)

In Bowhead Whale Genome portal, there was not information about human VEGF matching, so I run BLAST program, by comparing amino acid sequences of our interested protein of the two species. As a result:

Score	Expect	Method	Identities	Positives	Gaps
177 bits(449)	4e-64	Compositional matrix adjust.	98/119(**82%**)	107/119(**89%**)	0/119(0%)

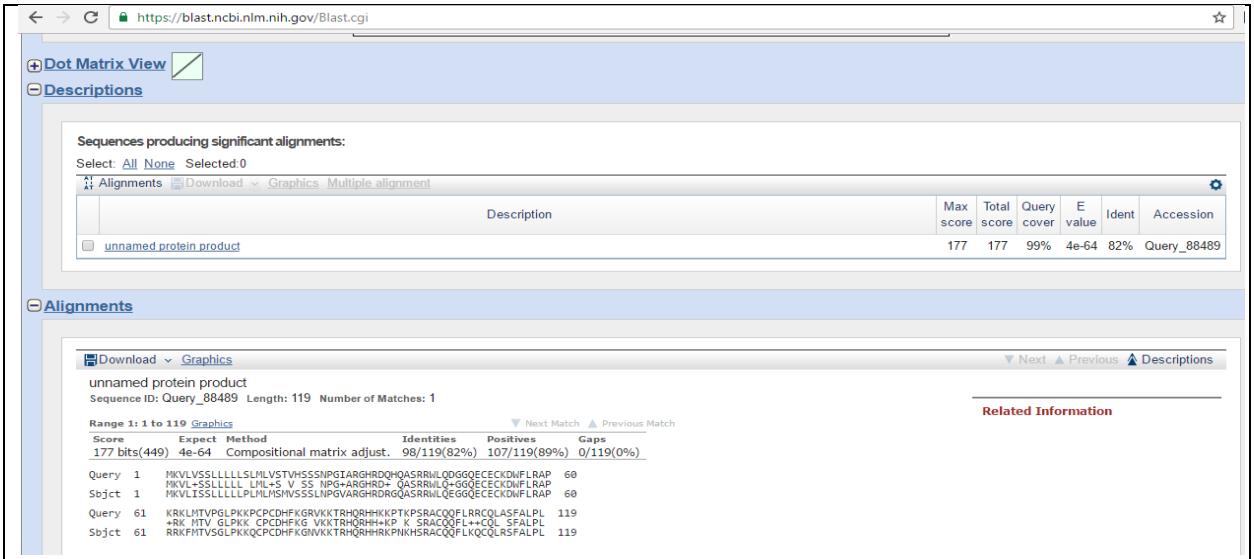

Figure 3. Blast results of human and bowhead VEGF co-regulated chekine 1 protein.[10]

According to outcome, 21 amino acid changes in VEGF co regulated chemokine 1 were observed, among them 12 amino acid had non-synonymous variation. These modifications could lead to specific features to the angiogenesis. There are also more proteins that responsible to new vessel formation in organism. So further research indeed necessary.

Related works:

For the cancer therapy, anti-angiogenesis drugs commonly used in clinics, especially vascular endothelial growth factor (VEGF) inhibitor agents most popular among cancer treating drugs. To give an example, Bevacizumab (Avastin®) is an antibody that specifically recognizes and binds to VEGF, so making it unable to attach and activate the VEGF receptor.[11] In addition, it was one of the first angiogenesis inhibitors, and showed positive results in medication, like halting tumor growth, and also could prolong cancer patient's life. There are other anti-

angiogenesis drugs, like sorafenib and sunitinib, which cease angiogenesis in different way: bind to receptors on the surface of endothelial cells or to other proteins in the downstream signaling pathways, blocking their activities [12].

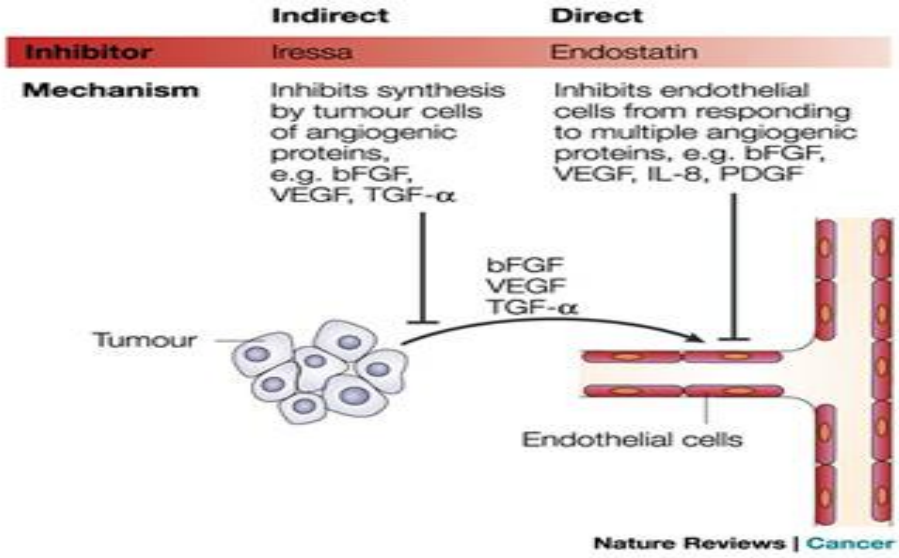

Fig.4. The way an angiogenesis inhibitors work

When the U.S Food and Drug Administration (FDA) gave approval to those drugs, it was known that anti-angiogenesis drugs would not have huge side effects. Nevertheless, present researches discovered that by inhibiting vessel formation process, in body takes place unfavorable circumstance, that decrease the effectiveness of the drug. Importantly, in heart cause to stroke or heart attack due to assembling of the clots in arteries, also there is disadvantages in fetal development, wound healing. Since those drugs stops function of the VEGF, those proteins have tendency to accumulate in the urine, cause kidney defects.

According to my hypothesis, if we used VEGF or other proteins, that themselves can control angiogenesis process, side effects like from anti-angiogenesis drugs would not occur. Bowhead whale's vessel system supplies huge whale organism and at the same time keep it in hypoxia condition.

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