COMMENTARY

What is a Cancer Cell? Why does it Metastasize?

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Abstract

This is a commentary on what a cancer cell is and why cancer cells metastasize. Normal cell get transformed to a cancer cell, with excessive production of free radicals that mutate the DNA of a normal cell. The immortality and malignant stage of transformed cell is maintained by higher GSH levels. With the faster rate of proliferation, when the cancer cell finds the place of origin is not conducive to its further growth, cancer cell chooses to take the metastatic course. We argue that if we can stop the exit of cancer cell from place of origin, cancer spread can be stopped or even cured.

Keywords: Metastasis - epithelial to mesenchymal transition (EMT) - matrix metalloproteinases - intravasation

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Introduction

Cancer is a dreaded disease and metastasis is usually the ultimate cause of death. In our previous article (Hegde et al., 2008) we had reflected on the origin of life in oxygen less atmosphere, the opposite complementary nature of plant and animal forms and why oxygen depleted plant forms, the vegetarian food, richer in antioxidants are more supportive to life. In this article we wish to extend the philosophy further particularly in the light of some recent findings what is a cancer cell and why metastasis? According to second law of thermodynamics cosmic force drives the universe towards increase in entropy. Life is order and death is disorder. Hence life is a miracle and aging, disease (cancer) and death is a certainty. The very act of respiration to derive energy from the food for sustaining life inevitably produces about 2% reactive oxygen radicals. These free radicals can attack and damage almost any vital molecules and structures in our body, irreversibly and permanently causing disease and death. So also these very free radicals can attack the DNA and transform normal cell to a cancerous cell. Obviously higher antioxidant levels within the cell can prevent the carcinogenesis.

It may also be noted here that our food habit and the non- availability of vital nutrients and good amounts of antioxidants in the food can be the major cause of cancer. As per the new Triage theory put up by Ames (2010) 'Nature always favors short term survival over long term survival'. It therefore follows that in the absence of adequate supply of essential nutrients, the vital processes such as energy production and protein synthesis and the vital organs such as heart are provided nutrients on priority and the processes such as DNA repair which does not pose immediate threat to life, may get a setback. The inability to effectively repair the DNA in these cells may become susceptible to cancerous transformation. It may not be surprising therefore heart cancer is very rare, almost unheard of. Our body is provided with antioxidant defense mechanism through the production of proteins such as superoxide dismutase, glutathione peroxidase, catalase etc that can effectively scavenge the free radicals. There are also low molecular weight antioxidants that mainly come from the food that can regulate the redox potential of a cell with the help of glutathione, the ultimate antioxidant within the cell. There is continuous battle between the oxidative stress produced by the free radical load and antioxidant defense in every cell of our body. Healthy levels of redox potentials are maintained by GSH: GSSG (reduced and oxidized forms of glutathione) the redox buffer by normal cells (Townsend et al., 2003). Unhealthy cells have lower levels of GSH which further decrease resulting in cell death. So also increase in GSH: GSSG higher than normal cell is necessary to transform normal cell to cancerous cell and confer the immortal status to cancer cell. We have shown that (Hegde et al., 2010) oral cancerous cells have higher GSH possibly to maintain malignancy and the precancerous cells even have higher levels of GSH, than cancerous cells perhaps to prevent them to become malignant.

Cancer cell however is an abnormal cell which is regarded as immortal, the cell that has forgotten to die. How this extraordinary ability is acquired by a cancer cell would be a very pertinent question to ask and seek the

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answer in order to prevent, control and if possible cure cancer. Normal human cells in cell culture die after ~50 cell divisions (Hayflick limit) (Hayflick, 1965). The main reason for this behavior is the loss of genetic stability due to progressive telomere shortening. Telomeres represent the linear ends of the chromosomes which shorten with every cell division (Zhang et al., 1999). Without the telomeres, the DNA cannot be replicated accurately, and must senescence (Bodnar et al., 1998). Tumor cells, however, cleverly develop counteractions to achieve immortality. For example, they activate the enzyme telomerase, a reverse transcriptase, which elongates the telomeres. Thus in cancer cells, the telomerase enzyme keeps rebuilding telomeres long past the cell's normal lifetime. The cells become "immortal", endlessly dividing, resulting in a tumor.

Now it is important to understand that what do convert the normal cells into cancer cells? The increase in oxidative stress leads to cell injury, necrosis or apoptosis-cell death. The excessive attack on the DNA of the cell, in the absence of sufficient antioxidant defense can lead to a transformation of a normal cell to a cancerous cell, which somehow confers on the cell the extraordinary status of immortality. In order to attain this cancer cell manages to keep the reduced GSH levels at a very high pitch so that the cell is never able to take apoptic or cell death course. Such a cancerous cell can originate in any part of our body and multiply without any check. To get the extra nutrients including oxygen the cancer cells may also get additional blood vessels through a process called angiogenesis. However this uncontrolled growth may not be possible to continue for long at the place of origin on account of the space restriction. Soon it may start feeling suffocation for the want of oxygen supply, a condition called hypoxia. In order to deal with this emergency situation, the cancerous cell may switch to anaerobic glycolytic pathway to generate energy for survival without oxygen. This is referred popularly as Warburg effect (Pani et al., 2010). This hypoxic condition sets in turn an alarm and elicits new protein synthesis by gene activation to enable cancer cells to detach and move to a new cozier place as the place of origin is no more conducive to its growth. There are series of biochemical reactions and processes that are enforced by the commanding cancer cells which results in metastasis, a process that enables the cancer cells to leave the place of origin to find a new place. In order to survive cancer cell takes this extraordinary metastasis course, cancer spreads and prospers till the host body succumbs to its onslaught.

An overgrown tumor can be a very hostile environment, due to shortage of oxygen and nutrients. Both hypoxia and inflammation promote metastasis (Bertout et al., 2008; Mantovani, 2009). It is now widely accepted that for metastasis, the basic engine for gliding or crawling of cancer cells is the actin cytoskeleton. Interruption of this property by flax lignan (Mali et al., 2012) can obstruct metastasis. Thus metastasis may ultimately represent an escape strategy from cell death. In general cancer cell metastasis comprises of an orderly sequence of pathological molecular events, collectively termed as metastatic cascade; starting with epithelial to mesenchymal transition (EMT), in which polarized epithelial cells are converted into motile mesenchymal cells and this is an essential prerequisite for metastasis; invasion of cancer cells through basal membrane into blood vessel (intravasation); survival of cancer cells in the blood stream; leaving the blood capillary and entering tissues of distant organ (extravasation); and colonization and multiplication to prosper in a new more cozy environment (Leber and Efferth, 2009; Feller et al., 2012). The microenvironment within the blood stream is hostile for circulating tumor cells and before they can find cozier environment. Cancer cells hide in the platelet cover, to protect themselves from stress and immune cells (Gay and Habermann, 2011). In advanced primary cancer, circulating tumor cells (CTC) can be found throughout the entire vascular system. When, where and how CTCs (seed) get successfully colonized (soil), as put forth by Paget, the seed and soil theory (Paget, 1889) is not fully understood and is currently the subject of intense study. It is therefore obvious that in order to effectively treat, manage, and cure cancer, the foremost important thing is to contain the cancer at the place of origin, with antimetastatic agents, where they may be more amenable for chemotherapeutic and radiological treatments. It is not surprising that research on antimetastatic agents is becoming the main focus for cancer therapy.

Conclusion

In conclusion it can be said that fast dividing cancer cells soon find the place of origin, hostile to their survival. They try to get out of this place in search of a new home. This involves multiple steps and if one can develop a successful strategy to house arrest them in the place of origin, soon they will die and not only cancer spread can be stopped perhaps it can also be cured.

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