HLA-G: A New Hope for Cancer Therapy?

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Whatever we know now has been a culmination of years and years of searching, registering, testing and proving. What our children take for granted, be it the internet or solar system, or our own knowledge of DNA and microbiology has been due to the efforts of thousands of years of searching, developing newer technologies and searching some more. The knowledge that we have now of DNA was always there; we just didn't know it existed until 60 years ago. Bacteria have been with us before our time, yet only through the invention of the microscope did our curiosity reach satisfaction. The fungus Penicillium had always grown on oranges, but only by studying its properties regarding bacteria did Mankind discover the wide range of antibiotics we have today. The answers to our problems have always been available; we just needed to use our knowledge, understand the problem, and reach new knowledge in order to "defeat" a problem.

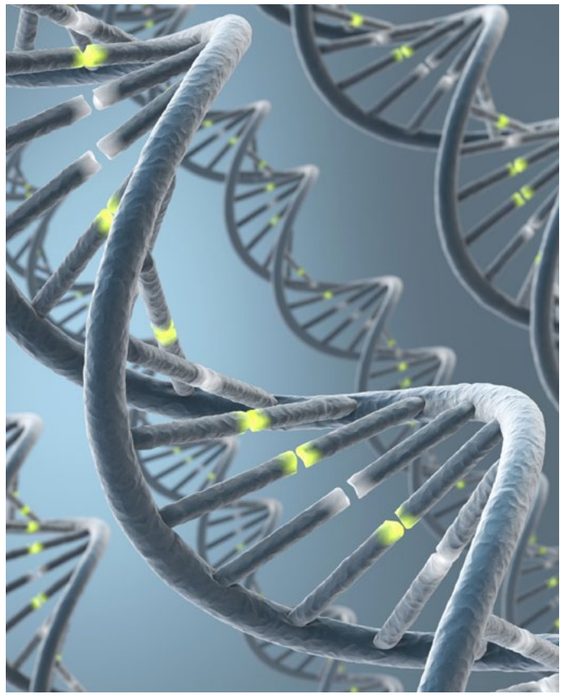
Throughout history, cancer has remained an enemy not fully understood and far from being defeated fully. Our three main weapons remain to be prevention (avoid risk factors), early detection, and chemo/radiotherapy. Many studies have shown us what the risk factors are regarding some common cancers like breast, colon, skin and lung. But there are many other tumors out there with unknown (if any) risk factors. Early detection scenarios have been many, and are increasing annually with our increase of diagnostic technology. From accurate CT scanners and MRI's to more and more accurate and studied tumor markers (HE-4, M2PK, f/T PSA, etc.), these have helped physicians rule out tumor presence and avoid anxiety in millions of patients worldwide. Although each diagnostic tool is not perfect on its own, it does provide a huge step forward in early cancer detection when compared to what knowledge we had only 50 years ago. Still, with all these tests, some cancers such as pancreatic CA and leukemia still evade our radar. Radiotherapy has had a lot of advancement in its technology, using narrower gamma-rays and more powerful computers to accurately "cut out" and destroy tumors. Chemotherapy has also seen many studies on how to be more effective against a tumor, while hurting less of our own normal cells. But tumor cells are very smart: some cannot be targeted with radiotherapy, while others have devised ways to resist chemotherapies by various mechanisms.

Around the year 2002, research into pregnancy mechanisms was under way to help improve IVF success rates. This research "stumbled" upon a genetic system that was soon to uncover an important question in biology: how does a fetus- who is genetically 50% "Father"- grow undetected while in contact with the mother's immune surveillance? Why doesn't the mother's immune system reject this "foreign body"? Was the placenta doing something to the mother's immunity so that the fetus can grow throughout pregnancy without being noticed? The answer came as YES! The genes responsible were eventually identified as part of our class-1 HLA (Human Leukocyte Antigen or MHC), and were named HLA-G. Activation of the HLA-G resulted in immune suppression, specially the Natural Killer (NK) cells.

Although Obstetricians want a good and active HLA-G for the sake of the survival of the fetus and success of pregnancy, it seems we-as already-born humans- usually don't. Only in a few instances has this gene been seen activated by our immune cells and that is to protect the body, or suppress it, against un-necessary antigens (a possible new approach to curing allergies/ auto-immune illnesses?).

With regard to cancer, however, the next question regarding HLA-G was obvious: it protects us during fetal life, but we still carry it inactive later on; therefore, does a growing tumor re-activate this gene system in order to grow while remaining undetected by our immunity??

The past few years have shown that many cancers do indeed have an active HLA-G. Studies also showed that the system produces 7 types of HLA-G proteins, 4 of which are membrane-bound (same as HLA-A or B or C), while 3 are soluble. They all do the same job: tell our immune surveillance that the cells producing these proteins are "OK" by suppression. So far, scientists have also identified at least 2 receptors for these proteins, the ILT-2 and ILT-4. Various tumors have been studied: melanoma, lymphoma (HD, NHL), acute leukemia, lung, SCLC, prostate, ovarian, bladder, colorectal and basal cell carcinoma. All have been shown to have an active HLA-G system, and the more active the gene is per tumor-cell population the more aggressive the tumor. What activates this system isn't fully understood yet, but scientists have already determined that an active immune system is needed to make the tumor turn on the HLA-G. Tumor cells grown in vitro eventually did not turn on the HLA-G, because there was no threat against their survival in this safe microenvironment. Studies also have shown that Interleukin-10 (IL-10) and hypoxia are also factors that turn on HLA-G. To add to the complication of this subject, recently, two newer HLA systems, also playing a suppressor role, have been discovered: HLA-E and HLA-F. Studies are still under way to understand more about their roles; scientists know that HLA-E supports HLA-G and that they work together, but what are their triggers, and how important are they for normal or tumor cells?



While all these studies are trying to understand this complex new system, some scientists are already asking the next question: if we attack HLA-G or block its action or shut down its gene, can we "unmask" a tumor. If we can do this, there is a good possibility that our immune system will detect the tumor and clear it out naturally. Moreover, this approach can be applied to many cancers. Can this knowledge (that was in front of us this whole time) be the answer to punching cancer in the face?

Many are hopeful; however, we need to understand the details of HLA-G and its companions. For example, will shutting it down also block some other necessary normal function of theirs? Currently, research into therapeutics against this system is nearly absent. It is also noteworthy that even if everything goes right and we have a cure, it still leaves out many patients who are immune-compromised. These patients will never benefit from this "cure".

To summarize, the discovery of the HLA-G,E and F systems has been like opening a Pandora's box . We are now understanding that the same genetic system that helps us thrive during pregnancy, could also be hijacked by tumors later on to avoid getting detected by our "police" while continuing to grow. But will their exposure to immunity help us in reaching a natural way of killing many cancers with 1 method?? I can say that we are still toddlers learning to walk here. The Olympic medal for sprinting is still far away. However, not trying is not an option.

In conclusion, our curiosity and search for knowledge has never stopped us from discovering new facts around us, testing new theories of unsolved puzzles, and being hopeful for darker mysteries still out there. The question now is: Will this HLA-G vs. Tumors be such a discovery?

Our will and curiosity should have an answer soon!