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Commentary on "Leukocyte-Cancer Cell Fusion-Genesis of a Deadly Journey"

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The main cause of cancer mortality is not the primary tumor itself but metastasis to distant organs and tissues, yet the mechanisms of this process remain poorly understood. Leukocyte–cancer cell fusion and hybrid formation as an initiator of metastasis was proposed more than a century ago by the German gynecologist Prof. Otto Aichel[1]. This proposal has since been confirmed in many animal models and more recently in three patients with malignant melanoma and two patients with renal cell carcinoma and two patients. Leukocyte–tumor cell fusion provides a unifying explanation for metastasis. While primary tumors arise in a wide variety of tissues representing not a single disease but many different diseases, metastatic cancer may be only one disease arising from a common, non-mutational event: fusion of primary tumor cells with leukocytes[2]. From the findings to date, it would appear that such hybrid formation is a major pathway for metastasis. Studies on the mechanisms involved could uncover new targets for therapeutic intervention. The three major forms of skin cancer are basal cell carcinoma which is not normally prone to metastasize, squamous cell carcinoma which can metastasize if left untreated, and malignant melanoma which is highly prone to metastasize and often fatal if not treated early[3].

Mechanisms of Cell-Cell Fusion

Much has been learned about the mechanisms cell-cell fusion between gametes, myoblasts, macrophages, trophoblasts, and epithelial cells in normal development and in diseases such as cancer[4,5]. While little is known about cell-fusion in cancer metastasis, in the normal systems above the fusion processes use similar membrane rearrangements. Proteins called "fusogens" work through different mechanisms. In some cases fusions are regulated by single fusogens, while in others several fusogens work in concert. In some cases fusions need to be present on membranes of both cells and in other cases only one of the membranes. Examples of such proteins are HA (Class I viral fusogen), p14 (FAST protiens or Class V viral fusogens), E1 (Fusexins or Class II viral fusogens), vSNARES, tSnares (endoplasmic fusogens), EFF-1 (Fusexins or FF), Syncytins (Class I viral fusogens), Atlastins (Dynamin or endoplasmic fusogen), HAP2/GCS1 (Fusexins), AFF-1 (Fusexins or FF), Myomaker (Multi-bass transmembrane proteins)[4,5]

As part of the process of cell-cell fusion, the membranes are first brought together to a distance of ~10 nm by fusogens. The mechanical force put forth by the fusogens and the subsequent lipidic rearrangements are the central features of fusion[5].

In cancer, once a macrophage or other leucocytic phagocyte has fused and hybridized with a primary cancer cell, why does it become metastatic? Although this remains largely unknown there is evidence that this is a matter of epigenetics—gene expression[6]. That is, some of the hybrid cells express the leucocyte genes for migration, homing to nearby lymph nodes and distant organs and tissues while at the same time maintaining the deregulated cell division of the cancer cell. If this should be the case, and it seems the simplest explanation, then targeting epigenetic expression would seem the best approach to stopping this process[6].

The word "cancer" is thought to be the most feared word in all cultures. At this writing the world is in a pandemic with the Corona 19 virus, which hopefully in the not too distant future should be contained with vaccines and treatments. On the other hand cancer is here to stay. One reason is heritable mutations in families that make them more prone to develop cancer, but contrary to popular belief this accounts for only 5-10% of cancers[7]. The main cause of cancer is new mutations in DNA such that cells go through de-regulated cell divisions. Many such mutations are caused by the environment, and with the skin this is largely from ultraviolet light from the sun or in tanning booths and the like. It can also be a matter of probability, for example the skin renews itself about every 4 weeks such that there are constantly dividing cells in the epidermis. Occasionally the DNA polymerase makes mistakes and mutations occur that can lead to skin cancer[8]. The mistakes are inevitable and are in fact the basic principle of evolution. In addition, mutations are not the only cause of cancer, for example translocations, single nucleotide polymorphisms, and epigenetic mechanisms such as DNA methylation play a major role.

Today, we are able to cure some types of cancer, and research is ongoing. Clinical trials and research studies are the key to finding definitive methods of prevention and now real durable cures in some cancers.

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