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Cancer hallmarks sustained by ectopic activations of placenta/male germline genes

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The acquisition of at least 8 new biological capabilities by cells characterizes the transformation from normal to malignant states.[1] Accordingly, cancer cells need to reprogram their genome to express these new biological properties. The question is therefore how could such a de novo and coherent gene expression program become active and operational?

A loss of the control of genetic stability leading to mutations as well as to minor and major genome rearrangements is very often considered as an essential element in the establishment of the diversity required to set up new functions driving cell transformation. Profound alterations of the cancer cell epigenome also systematically accompany oncogenic transformations and clearly contribute to the establishment of the indispensable cancer gene expression profile and its relative stability over time.[2] Recent investigations are now demonstrating that cancer cells also largely use their reservoir of normal silent genes to acquire these new biological capabilities by activating a variety of unscheduled gene expression programs. The genes ectopically activated during the process of malignant cell transformation, due to genetic or epigenetic upheavals, have the potential to provide the cells with de novo molecular pathways required to develop new capabilities.[3] One could postulate that many genes sustaining cancer hallmarks could simply be normal silent genes, present in the genome of all cells, but whose expression is normally restricted to a given cell type or a specific developmental stage. Recently, we demonstrated that male germ cells express the largest number of tissue-restricted genes, and that many of them become ectopically reactivated in almost any cancer.[4] Therefore, cells in the course of malignant transformation have the possibility to "open" their male-specific genes "reservoir" to take various building blocks required to achieve new functions. Important questions would then be why do male germ cells use such a large number of specific genes? Why are these genes strictly "locked" in a repressed state in all somatic cells? How could the "out of context" functions of these genes help malignant transformation?

Male germ cells are unique in the whole organism not only because they undergo genome-wide meiotic genes and chromosomes shuffling, but also because they activate a highly specialized genetic program leading to the generation of the only cells capable of leaving their production site to "travel" into the hostile environment of another organism. The acquisition of these extraordinary functions relies on specific genes, among which some are specialized to act on the genome and profoundly alter its organization. In particular, after meiosis, there are specific factors directing a genome-wide histone hyperacetylation, followed by genome-wide histone removal and assembly of new DNA-packaging structures.[5] Most of the underlying drivers are themselves testis-specific, such as Brdt,[6] and can be aberrantly activated in cancers.[4] It is hence foreseeable that, among other actions, the ectopic activation of these factors could create a ground for a sustained alteration of the genome/epigenome and a subsequent stably modified state of gene expression. The use of an elegant model of inducible tumorigenesis recently provided us with a solid basis for this hypothesis. Indeed, in an inducible brain tumor model in Drosophila, malignant transformation was not only associated with, but also highly dependent on, the ectopic activation of a variety of germline-specific genes.[7] In the case of human lung cancers, we observed that, among several hundreds of ectopically activated male and placental specific genes, 26 were tightly associated with the most aggressive and metastasis-prone tumors.[4] It is not known whether the activation of these genes is actually required to sustain tumor aggressiveness, but it clearly identified tumors presenting striking common features, despite being of various histopathological origins. These aggressive tumors show highly increased expression levels of genes encoding nuclear factors fueling cell proliferation while downregulating genes encoding membrane and signaling factors, many involved in the immune response. This "aggressive" gene expression profile can support at least two of the acquired properties of cancers, i.e., avoiding immune destruction and pushing cell proliferation. It can be therefore predicted that these newly acquired properties directly depend on the underlying ectopically activated genes. Following the hypothesis that cancer cells use the ectopic gene expression to establish new functions, it can be proposed that lung cancer cells become "addicted" to these factors. The situation would be somehow similar to Drosophila brain tumors, where cell proliferation becomes dependent on some of the ectopically activated

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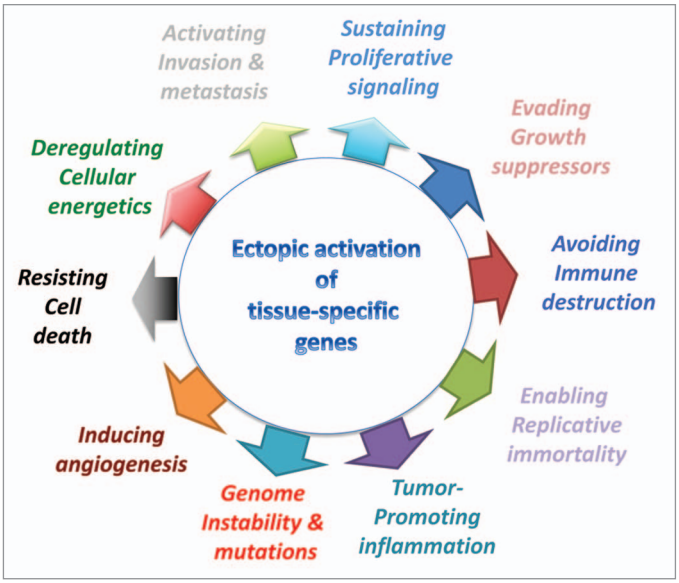

Figure 1. The observation of a large-scale activation of normally silent tissue-specific genes and the demonstration of their critical contribution to the characteristics of malignant cells is at the basis of a working hypothesis, which postulates that the "out of context" activity of various normally silent genes, is essential to support the acquired capabilities of cancer cells. The figure was inspired by Hanahan and Weinberg.[1]

germline genes.[7] The extinction of ectopic gene activations, which very likely help all cancer cells to maintain their malignant states, could therefore be a very promising therapeutic approach. Our very recent work brings a proof of principle for this hypothesis in diffuse large B cell lymphoma (DLBCL). Indeed, we found that the overexpression of a specific gene, CYCLON, which is normally predominantly expressed in testis, is associated with a poor response to chemotherapy in combination with the monoclonal therapeutic antibody Rituximab, the current standard treatment for this malignancy. Most, importantly the downregulation of CYCLON by pharmacological means restored sensitivity of the tumor cells to Rituximab.[8] Therefore, a promising field of research would be the understanding of the mechanisms underlying ectopic gene activations in cancer and the determination of critical elements allowing their extinction. (**Fig. 1**)

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