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Molecular mechanism of the "feedback loop" model of carcinogenesis

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It is commonly accepted that cancer is a genetic disease. The current prevailing theory of carcinogenesis is the somatic mutation theory of carcinogenesis and metastasis (SMT). This theory postulates that mutations in epithelial cells lead to uncontrolled proliferation of tumor cells in a cell-autonomous fashion. This cell-autonomy is increasingly criticized. Current data suggest that the tumor microenvironment is also strongly involved in carcinogenesis. Recently, we published a hypothesis that considers the important contribution of the tumor microenvironment in carcinogenesis and complements the classical clonal evolution model.

Essentially, this "feedback loop model" (FBM) postulates that the physiological communication between cancer cells and stromal cells in inflammatory or proliferative conditions is altered by anomalous signal processing within the parenchymal cells. The inability of parenchymal cells to correctly finalize the intercellular communication might result in a perpetuation of the activated state of cells and the tumor micromilieu. The FBM is unique among the tissue-based models because in this model tumor and stromal cells interact together in a reciprocal manner to form the cancer phenotype. Contrary to the SMT, the FBM postulates that mutated genes act in a cell-heteronomous fashion, not in a cell-autonomously fashion.

The Feedback Model of Carcinogenesis

The somatic mutation theory of carcinogenesis and metastasis (SMT) is the currently prevailing concept of carcinogenesis. It states that malignant transformation is initiated by acquisition of a gate-keeping mutation in a replication-competent cell and then driven by further accumulation of mutations in a multistep process.[1,2] The mutations thereby act in a cell-autonomous manner and the role of the microenvironment is subservient to that of the original mutated cell.[3]

This concept was criticized because the accumulation of the at least three to six mutations that are necessary for a cell to become "malignant" might not be achieved in the normal life span of a single cell.[2,4,5] Furthermore, it could be experimentally shown that the neoplastic phenotype is reversible. Isolated parenchymal cells from neoplastic tissues reversed their phenotype when transplanted in normal tissues.[3,6,7] Today, cancers are rather considered as heterogeneous and structurally complex organs, and more credence has recently been given to additional cell types that contribute to the carcinogenesis and pathophysiological properties of tumors.[8-11] A large number of the pathophysiological features of cancers can better be explained by reciprocal interaction between the parenchyma and the stroma than by accumulation of an undeterminable number of mutations of the cancer cell.[3] This perception has led to newer, tissue-based theories of carcinogenesis. The tissue-based concepts postulate that transformed cells are not completely autonomous but can be affected by signals from stromal cells.[3,8] However, although there seems to be evidence for the tissue-based approach in solid tumors, there is no new concept for the molecular mechanism of the malignant transformation of cancer cells.[9-11] Recently, we published a new

hypothesis on the mechanisms that might underlie early carcinogenesis, the feedback loop model (FBM).[12]

Molecular Mechanism of the New Model

The name "feedback model" refers to the intercellular mechanisms that emphasize the new hypothesis of carcinogenesis. The reciprocal communications between stromal and parenchymal cells in inflammatory or proliferative conditions can be considered as feedback loops. These feedback loops are physiologically controlled by intracellular signaling processing mechanisms that filter, damp or limit these interactions. This eventually terminates the proliferative or inflammatory conditions. According to the FBM, mutations in parenchymal cells might interfere with these regulatory mechanisms. Mutations in parenchymal cells might result in a dysfunctional intracellular signaling processing and thereby indirectly in an aberrant response to extracellular stimuli. The lack of regulation by parenchymal cells could lead to a perpetuation of the proliferative or inflammatory states within the tumor micromilieu.[12] The consequence of this model is that mutations in cancer cells do not act in a cell-autonomous manner, but in a cell-heteronomous fashion.

Dynamic of the System

An important question is how stable such a feedback loop would be. Clinical studies examining spontaneous tumor regression found a much higher frequency of histological frank carcinomas than should be suspected in post mortem examinations. These studies showed that 34% of men in their forties had prostate carcinomas, and 39% of women in their forties had breast cancers.[13,14]

An intrinsic problem of our hypothesis is that positive feedback tends to cause system instability. When there is more positive feedback than there are stabilizing tendencies, there will usually be divergences from equilibrium. A loop system might ramp up to extreme values, which may destroy the system and abrogate tumor growth.[15] Therefore, stabilizing factors are necessary. A possibility to stabilize the feedback could be additional mutations in other signaling pathways. Most of the common mutations in cancers are diagnosed in fully developed tumors and thus are unlikely to shed light in the events that initiate carcinogenesis. However, these mutations could be responsible for the stabilization of the feedback loop.[3,16]

Another point is that the FBM is dependent on soluble extracellular factors, because these factors mediate the information flow. Because of this, a major alteration of the extracellular milieu could also cause a collapse of the feedback loop. This may be the underlying mechanism of oncolytic virus therapies.[17] In this respect, more stability could be achieved by tumor growth, because with increasing size the disturbing influence of extrinsic factors will be smaller.

To conclude, FBM is a new the tissue-based hypothesis on early carcinogenesis. Mutations according to the FBM act in a cell-heteronomous fashion to form a positive feedback loop between parenchymal and stromal cells. The proposed new model has a more unpredictable dynamic than the classical SMT, where mutations always lead to proliferation and cellular activation in a cell-autonomous manner. However, this unstable dynamic might be in good accordance to clinical data.

References

1. Bergers G, Hanahan D, Coussens LM. Angiogenesis and apoptosis are cellular parameters of neoplastic progression in transgenic mouse models of tumorigenesis. Int J Dev Biol 1998; 42:995-1002; PMID:9853830.
2. Vogelstein B, Kinzler KW. Cancer genes and the pathways they control. Nat Med 2004; 10:789-99; PMID:15286780; http://dx.doi.org/10.1038/nm1087.
3. Sonnenschein C, Soto AM. The death of the cancer cell. Cancer Res 2011; 71:4334-7; PMID:21507929; http://dx.doi.org/10.1158/0008-5472.CAN-11-0639.
4. Renan MJ. How many mutations are required for tumorigenesis? Implications from human cancer data. Mol Carcinog 1993; 7:139-46; PMID:8489711; http://dx.doi.org/10.1002/mc.2940070303.
5. Cho KR, Vogelstein B. Genetic alterations in the adenoma--carcinoma sequence. Cancer 1992; 70(Suppl):1727-31; PMID:1516027; http://dx.doi.org/10.1002/1097-0142(19920915)70:4+<1727::AID-CNCR2820701613>3.0.CO;2-P.
6. Bissell MJ, Radisky D. Putting tumours in context. Nat Rev Cancer 2001; 1:46-54; PMID:11900251; http://dx.doi.org/10.1038/35094059.
7. Hendrix MJ, Seftor EA, Seftor RE, Kasemeier-Kulesa J, Kulesa PM, Postovit LM. Reprogramming metastatic tumour cells with embryonic microenvironments. Nat Rev Cancer 2007; 7:246-55; PMID:17384580; http://dx.doi.org/10.1038/nrc2108.
8. Kenny PA, Lee GY, Bissell MJ. Targeting the tumor microenvironment. Front Biosci 2007; 12:3468-74; PMID:17485314; http://dx.doi.org/10.2741/2327.
9. Pupa SM, Ménard S, Forti S, Tagliabue E. New insights into the role of extracellular matrix during tumor onset and progression. J Cell Physiol 2002; 192:259-67; PMID:12124771; http://dx.doi.org/10.1002/jcp.10142.
10. Bissell MJ, Hines WC. Why don't we get more cancer? A proposed role of the microenvironment in restraining cancer progression. Nat Med 2011; 17:320-9; PMID:21383745; http://dx.doi.org/10.1038/nm.2328.
11. Radisky D, Hagios C, Bissell MJ. Tumors are unique organs defined by abnormal signaling and context. Semin Cancer Biol 2001; 11:87-95; PMID:11322828; http://dx.doi.org/10.1006/scbi.2000.0360.
12. Rückert F, Grützmann R, Pilarsky C. Feedback within the inter-cellular communication and tumorigenesis in carcinomas. PLoS One 2012; 7:e36719; PMID:22615799; http://dx.doi.org/10.1371/journal.pone.0036719.
13. Sakr WA, Haas GP, Cassin BF, Pontes JE, Crissman JD. The frequency of carcinoma and intraepithelial neoplasia of the prostate in young male patients. J Urol 1993; 150:379-85; PMID:8326560.
14. Nielsen M, Thomsen JL, Primdahl S, Dyreborg U, Andersen JA. Breast cancer and atypia among young and middle-aged women: a study of 110 medicolegal autopsies. Br J Cancer 1987; 56:814-9; PMID:2829956; http://dx.doi.org/10.1038/bjc.1987.296.
15. Franklin G. Feedback Control of Dynamic Systems. Prentice Hall, 2002.
16. Stratton MR. Exploring the genomes of cancer cells: progress and promise. Science 2011; 331:1553-8; PMID:21436442; http://dx.doi.org/10.1126/science.1204040.
17. Kasuya H, Takeda S, Nomoto S, Nakao A. The potential of oncolytic virus therapy for pancreatic cancer. Cancer Gene Ther 2005; 12:725-36; PMID:15818382; http://dx.doi.org/10.1038/sj.cgt.7700830.