Hypothesis/Commentary

An Interlocker Concept of Carcinogenesis

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Abstract

A critical feature in the sequence of events occurring during carcinogenesis is the development of irreversibility. The term “Interlocker” is used here to denote a mechanism by which irreversibility is brought about. The presentation focuses on conceptualizations of such processes. Two will be described below. (Cancer Epidemiol Biomarkers Prev 2006;15(8):1425–6)

The first concept is built around the occurrence of several common features found in cancers of solid organs. These include a loss of control of cell proliferation, disorganization, and infiltration. The concept is that the Interlocker is like a collar, which binds together these common features irreversibly into a whole entity. It becomes fully active at the transition of precancer to cancer. The concept is simple and leads to important consequences. The first of these is that it presents a target for chemoprevention of cancer and the second is that a knowledge of the composition of such a collar potentially could lead to strategies for its disruption and cancer therapy during its early phase.

The concept is highly attractive but information about the nature of the collar is deficient. One possibility is that the Interlocker involves aberrant glycoproteins. Supporting this conjecture are two lines of investigation. One is the finding of aberrant glycoproteins during carcinogenesis. These glycoproteins contain structural changes in their side chains, in particular increased β1-6 branching asparagine-linked oligosaccharides. The changes are found in cancers of a number of organs, including breast, large bowel, lung, esophagus, and melanoma (1-9).

A second line of investigation has been into the increased expression of N-acetylgalactosaminyltransferase V, which is also found in cancers of a number of these organs as well as others (10-14). The association of glycoprotein defects with cancer is impressive as documented in the publications cited. Assuming that this represents a significant component of the Interlocker, the point of which the aberrations result in loss of reversibility would require elucidation.

The second concept of an Interlocker is quite different. Central to this concept is the understanding that a critical feature of cancer is disorganization. An important manifestation of this disorganization is loss of cell/cell adhesions. A striking finding in this regard is the loss of E-cadherin cell/cell adhesions. A considerable amount of information exists pertaining to this adhesion protein. Its loss is related to carcinogenesis in several tissues, including lung, breast, liver, colon, esophagus, stomach, pancreas, head and neck, and skin (15-22). In addition to binding cells together, E-cadherin is closely allied with catenins, actin filaments, and intracellular signaling pathways (17-19, 23, 24). Thus, E-cadherin loss or dysfunction as an Interlocker not only could result in impaired cell/cell contact but also be accompanied by differing degrees of malignant manifestations depending on the nature of alterations in the closely related signaling factors.

Summary. This article puts forth the conceptualization that irreversibility in carcinogenesis can be the result of an Interlocker. Two examples are discussed, one termed as a collar, binds together features of carcinogenesis so as to form an irreversible entity. The second is the loss or dysfunction of cell/cell adhesions with evidence that this can be due to E-cadherin. The existence of an Interlocker would be important for several reasons. For cancer prevention, it could provide a target for intervention and one existing until a late point in the progression of precancer to cancer. For a collar type of Interlocker, an agent that would break the collar could convert the lesion from being irreversible to being reversible, at least early in cancer. Finally, the conceptualization of the existence of Interlockers itself is of value in providing new areas of research and new ways of evaluating data.

References

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