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A Unifying Hypothesis Concerning the Nature of Malignant Growth

(transport/cell surface membrane/limiting nutrients/regulation/cell cycle)

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ABSTRACT **It is suggested that the crucial change in a malignant cell is an alteration in the cell surface membrane that results in increased internal concentrations of nutrients that regulate cell growth.**

Many observations suggest that the growth of mammalian cells *in culture* can be influenced by the availability of certain low molecular weight nutrients (1). For example, "normal" cells lines often grow to higher densities in growth medium that has been enriched with low molecular weight nutrients*. These observations are puzzling if it is assumed that cells grow in response to a special "signal" to grow, or stop growing in response to an inhibitory "signal." Also, specific nutrients, such as glutamine and isoleucine (2, 3), putrescine (4), and zinc (5, 6), regulate cell growth under special conditions. Deficiencies of these nutrients can arrest cell growth in the G_1 phase of the cell cycle†.

I wish to propose that these observations are actually representative of the normal situation. That is, I suggest that the growth of mammalian cells may, in fact, be regulated quite commonly by the availability, inside the cell, of one or more of the nutrients required for growth‡. In other words, it is suggested that mammalian cells do not normally require an additional "signal" to grow if all nutrients are present at sufficient concentrations inside the cell.

If one assumes that concentrations of critical nutrients inside the cell regulate cell growth *in vivo*, one is confronted with the question of how growth can be controlled selectively in different tissues, since the blood levels of low molecular weight nutrients are relatively constant throughout an animal. Selectivity of control of growth of different cells could be accomplished by selectively altering the availability of the nutrients inside the cells. In other words, selectivity of growth control in an intact animal could be by way of transport systems at the cell surface membrane. These, in turn, would be regulated by hormones or growth factors. The suggestion then is that the growth of normal cells *in vivo* is controlled by hormones or growth factors§ that influence the uptake or availability, inside the cells, of the specific nutrients that in turn actually regulate growth. Thus, growth stimulation would result from stimulation of uptake and growth inhibition would result from inhibition of uptake of the critical nutrients.

Consistent with this view is the evidence that polypeptide hormones that act at the cell surface control growth in at least some instances *in vivo* (7). In laboratory culture, growth of "normal" cells requires serum, and much evidence suggests that serum contains a complex mixture of growth factors (8–11), at least some of which affect uptake (12–14).¶ It is clear that a relatively small number of critical nutrients could, because of the many different combinations possible, give selectivity in control of growth of different cell types. It is also clear that in a marginal situation in which concentrations of hormones and internal availability of nutrients are almost sufficient for growth, a slight change in the cell surface membrane, or even increased cell motility, might be sufficient to increase internal concentrations of critical nutrients and initiate growth. Thus, there could be great selectivity and sensitivity of a growth regulatory mechanism based on concentrations of critical nutrients inside the cell.

These considerations have led me to the hypothesis that cancer results from changes in uptake mechanisms caused by changes in the cell membrane. These changes would make critical nutrients, which normally limit growth, available at higher concentrations inside a cell. In other words, it is suggested that the primary cause of malignant growth is the increased concentrations of these critical nutrients inside the cell.

This hypothesis suggests that different types of cancer cells will vary widely and will be uniform only in having altered cell membranes that affect uptake mechanisms. For example, malignant growth might result from an increase in the amount of a transport protein, or from an increase in the activity of the protein. It might also result from a structural

* 3T3 cells grow (unpublished observations) to double the cell density if a supplement of F12 and McCoy's medium constituents is added to Eagle's medium, though the cell density attained remains proportional to the amount of serum in the medium (see ref. 8).

† Deficiencies of some nutrients under certain conditions can lead to cell death rather than quiescence. Such nutrients are not of primary concern in the present discussion, though the possibility remains that these nutrients may be involved in regulating cell growth in other instances.

‡ The word "nutrients" is used broadly to include all the low molecular weight materials that enter the cell.

§ The concentrations of the hormones or growth factors would be regulated by mechanisms beyond the scope of this discussion.

¶ It is known (ref. 12) that the addition of serum stimulates uptake of phosphate in quiescent 3T3 cells. We have now found that phosphate can regulate the growth of 3T3 cells. In media of high serum concentration, limiting phosphate appears to arrest the growth of 3T3 cells in G_1 phase, and growth can be reinitiated by the addition of phosphate. Details of these experiments will be published in the near future.

change in the membrane or from a change in cyclic AMP metabolism, either of which might secondarily increase the activity of the transport protein. Alternatively, malignancy might result from an increase in the availability or in the affinity of specific hormone-receptor sites. A still different cause might be a structural change in a cell membrane that increases permeability. Still another possibility would be a membrane change that results in greater cell motility, if that increases uptake. The membrane changes in turn could be caused by many different mechanisms (viruses, radiation, chemicals), though mechanisms operating at the genetic level would be likely because of the stability of the change. Whatever the molecular change in the membrane, and whatever the mechanism that caused it, malignant growth would actually result from the increased concentrations of critical nutrients inside a cell.

The hypothesis is consistent with the observation that different cancers have widely different growth rates, varying from very slow to completely unrestricted growth. These variations would correspond to changes in concentrations of critical nutrients, inside the cell, in all gradations from the normal limiting levels to unrestricted, maximum availability. Also, a gradual accumulation of membrane changes could lead to increasing malignancy, in small gradations or abruptly.

Finally, the hypothesis focuses attention on uptake mechanisms as possibly being the primary growth regulatory mechanism in mammalian cells *in vivo*, emphasizes the importance of studies of these uptake mechanisms, as well as of studies of the changes in uptake that are known to take place in malignant cells (15–20), and predicts that in instances in which the level of nutrients can be manipulated it should be possible (21) to arrest growth of malignant cells in the G_1 phase of the cell cycle by limiting some critical nutrient. In particular, the suggestive evidence (1–6, 21) that a wide variety of nutrients can have regulatory functions in mammalian cells deserves exhaustive study.

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