THE ROLE OF MYOSIN AND ACTIN IN CARCINOGENESIS: AN HYPOTHESIS

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Abstract

The theory is advanced that cellular processes have a cyclic nature controlled by a periodic charge exchange between actin and myosin, regulated by the oxidation and reduction of sulphydryl moieties. Cellular characteristics and control including mitosis are determined by the redox state of these two proteins; mitosis being determined by both the amplitude and period of the thiol cycle. It is proposed that all carcinogens induce an oxidation of specific myosin sulphydryl units with a concomitant reduction of specific actin sulphydryl units. They thereby initiate a thiol cycle of increased magnitude which leads to mitosis. This theory leads to predictions concerning the manner in which reducing agents and hyperthermia should be used in the prevention and treatment of cancer.

1. REGULATION OF ACTIN-MYOSIN SYSTEM (A-M SYSTEM)

In the past few years it has become evident that actin and myosin have a significant role not only in muscle function but in nearly all cellular phenomena.

Given the importance of the A-M system, understanding of its regulation is necessary. It is generally believed that the muscle A-M system is regulated via intracellular Ca^{++} and the regulatory proteins. However, there is evidence to show that Ca^{++} plays a secondary role and that contraction can take place in the absence of Ca^{++}, or in the presence of low Ca^{++} concentration, when the ATP and Mg^{++} concentrations are low or when oxidizing and SH reagents are present. Furthermore, relaxation involves some process other than removal of Ca^{++} and, for Ca^{++} sensitivity of the A-M system, myosin SH s are essential[1]. The fact that all relaxing agents, either directly or indirectly, protect the myosin SH groups and that oxidizing agents, SH reagents and flavin antagonist inhibit relaxation[2] indicates the necessity of myosin SH groups for regulation.

It has been known for some time that at contraction the SH of the globular head of myosin, where the functional SH groups, SH_1 and SH_2 are found, decrease and at relaxation increase. Lately, it has been shown that at contraction the reactivity of cys-10 of F-actin is increased and the reactivity of SH_1 of myosin is decreased. At relaxation the converse takes place[3].

It has also been shown that the low rate of ATP cleavage in resting muscle results from the formation of a ring structure involving the SH_1 and SH_2 of

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myosin and Mg APT. The association of myosin with actin is a process where the ring is opened through binding of actin at or near the nucleophilic site SH_1, thus accelerating energy conversion[4].

Sakai[5] found that the cyclic variation of acid soluble SH groups in sea urchin eggs was due to protein bound SH. A water soluble and an acid soluble protein were isolated which behaved like actin and myosin respectively. He also found that the strands made from the acid soluble protein contracted under the influence of oxidizing agents or the water soluble protein but elongated under the action of reducing agents. Furthermore, the interaction between the water soluble protein and the acid soluble protein is by means of SS-SH exchange. Contraction is accompanied by oxidation of the SH groups of the thread and reduction of the water soluble protein, contractility being directly proportional to the SH concentration of the acid soluble protein available for oxidation. Elongation is brought about by the reverse process. He also observed that this charge transfer takes place between the acid soluble proteins and the spindle, and that it involves only the free SH groups. Sakai found that the SH groups of the acid soluble protein decrease after fertilization, reaching a minimum about the middle of G_1, then increase to a maximum value in late S and again decrease at mitosis, whereas the SH groups of the water soluble protein change reciprocally.

It can therefore be deduced that:

(a) the acid soluble protein is myosin,
(b) the A-M system is regulated by charge transfer between the two proteins,
(c) myosin can be found in two states — a "charged" state in which its sulphydryl-MgATP ring is intact, and an "uncharged" state where the ring is broken,
(d) the ring can be broken by interfering with any of its components, i.e. decreasing the Mg^{2+} concentration, decreasing the ATP concentration or by chemically blocking or oxidizing its SH groups,
(e) when the ring is broken and a charge transfer takes place between the myosin and actin, ATP hydrolysis and contraction occurs,
(f) for relaxation to take place myosin has to be charged again, i.e. myosin has to be reduced and ATP synthesized in the presence of Mg++,
(g) Ca++ could induce contraction by directly or indirectly interfering with the myosin SH groups, by competition for ATP, or both,
(h) Na^+ permeability and thus of substrate is determined by the phosphate and redox state of the A-M system,
(i) there is a periodic charge transfer between actin and myosin (thiol cycle) during the cell cycle,
(j) the thiol cycle is indispensable for division.

2. DNA REGULATION

It is believed that the DNA is regulated by the nuclear proteins, histones and non-histone chromosome proteins (NHCP). The control by these proteins is considered to be non-specific. However, although histones do not vary in concentration during the cell cycle, their thiol and phosphate status does, having maximum SH and phosphate in the S-phase and minimum in G_1[6]. These authors do not exclude the possibility that this protein could be related

to the acid extractable contractile protein described by Sakai. This is also suggested by the fact that histones combine with actin and induce actin polymerization[7].

Even if they are not related to myosin, their thiol and phosphate state could still be regulated via the A-M system. It has been established that NHCP contain actin and myosin; that histone binding to DNA is influenced by NHCP; and that histones interact with NHCP via SS bridges.

It can be concluded that DNA synthesis and transcription is controlled by the redox state of the membrane A-M system which, in turn, influences cytoplasmic A-M, NHCP and histones, differentiation being obtained either by anisotropic arrangement of actin and myosin or by different degrees of actin and myosin interaction or both.

3. EFFECTS OF CARCINOGENS ON A-M AND ITS REDOX

The effects of mitotic agents on the acid soluble SH have been known for some time. A number of authors observed that mitogens, including carcinogens, induce a decrease in acid soluble SH followed by an increase.

At present there is ample evidence to show that mitotic agents as diverse as insulin, partial hepatectomy, estrogen and radiation induce this cyclic variation in acid soluble SH groups and that all carcinogens are electrophylic.

It is generally agreed that ATP synthesis is the result of the oxidation of electron donors but controversy exists as to the nature of the coupling device[8], although in all hypotheses an ATPase (F_1), whose nature has not been identified, is supposed to be involved. However, the A-M system, regulated as proposed above, could satisfy the requirements of the energy transducer and explain the F_1 conformational changes; Williams' "high energy" protons being the SH of the "charged myosin" and Mitchell's proton gradient being a secondary event, regulated by the redox state of the A-M system. It can be concluded that:

(a) cellular metabolism is regulated by the redox state of the A-M system,
(b) the primary action of carcinogens and other mitotic agents is on the A-M system; by their electrophylic nature they induce charge from myosin to actin and thus contraction,
(c) when contraction is neither so high as to induce osmotic cytolysis due to the very high increase in permeability, or to make the cell dormant, nor so small as to leave the cell in G_o, the cell will proceed to G_1,
(d) the contraction in G_1 will lead to an increased substrate uptake and metabolism which, in turn, will lead to a greater relaxation in S than in G_o; this, in turn, leads to minimum permeability and metabolism late in S, and thus to a maximum contraction and division in M,
(e) once the cell is activated it will continue to divide unless relatively high doses of reducing or oxidizing agents are present; the reducing agents will either induce death by starvation or revert the cell to G_o, where the cell will have a thiol cycle with different amplitude and period from that necessary for division; the oxidizing agents will either induce death by cytolysis or make the cell dormant (contracted).

4. CANCER PREVENTION AND TREATMENT

It follows that cancer can be prevented and treated by destroying the thiol cycle using either high doses of alkylating and oxidizing compounds or antioxidants. Apart from surgery, current cancer treatments involve the use of the former.

There is evidence to suggest that the mechanism of action of hyperthermia is similar to that of antioxidants. This suggests that hyperthermia and antioxidants, alone or in combination, may prove to be a more effective way of treating cancer. There is increasing evidence to support this proposal.

5. CONCLUSIONS

The A-M system, its spatial distribution and its conformational changes induced by its oxidoreduction and phosphorylation-dephosphorylation, appears to be the unifying factor in cellular division, differentiation, muscle contraction, impulse transmission, transport, metabolism and indeed the basis for its biological function.

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Reviewer Comment

Perhaps the author should note that, although an anomalous thiol cycle may result in cellular injury and even stimulate mitosis, it doesn't necessarily follow that a permanent change will be passed on to daughter cells. Moreover, the effects of the carcinogen on the thiol cycle have to be perpetuated long

after its removal and despite the production of new myosin and actin molecules by the affected cell.

The other points that should be taken into consideration are that actin and myosin are largely found in the cytoplasm and, generally, actin tends to predominate. It is likely, therefore, that most of the effects of the abnormal thiol cycle are likely to be cytoplasmic.

In enunciating cancer prevention and treatment, perhaps the importance of the thiol cycle in causation should be somewhat reduced while its importance in treatment should perhaps be emphasized.

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Author's Reply

I agree that not all changes in the thiol cycle will lead to division. Different changes will lead to different pathological conditions. For division to take place, a thiol cycle of certain values of amplitude and period has to ensue.

If the myosin and actin in the daughter cells are new or old is not important for the perpetration of the carcinogenic effect. The important thing is their redox state, i.e., once this special coupled oscillation is activated for cancer to take place the environmental condition should be such as to permit the repetition of this special thiol cycle. Thus, if the daughter cell finds itself in a very low PH or strongly reducing environment, the relatively high contraction required in G_1 will be inhibited and the daughter cell will not divide and thus no cancer will ensue.

The carcinogens however do not affect only the cell activated to divide but also produce some oxidation in the neighbouring cells and immediate environment, thus creating suitable conditions for the division of daughter cells.

As far as the distribution of myosin and actin are concerned, although the actin/myosin ratio in non-muscle cells is believed to be double that in muscle, myosin is found in all non-muscle cells and, although these two proteins are abundant in the protoplasm, they are not exclusive to it. Thus they have been found in cellular membranes, plasma membrane, nucleus, nucleoli mitochondria, cellular surface, non-chromosome proteins, etc., and they play an essential role, not only in cytoplasmic movement, but cellular adhesiveness, membrane stability and integrity, capping of surface membrane receptors, pinocytosis, phagocytosis, exocytosis, endocytosis, etc.[1-7]

I did not put too much emphasis on treatment for two reasons:

1. I thought that the chance of publication would be better if the paper was short; and
2. I tried to put emphasis on the mechanism, thinking that once the mechanism is known the treatment will follow.

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