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ADVANCES IN RADIATION BIOLOGY – HIGHLIGHTS FROM 16TH ICRR SPECIAL FEATURE: REVIEW ARTICLE

A hypothesis: radiation carcinogenesis may result from tissue injuries and subsequent recovery processes which can act as tumor promoters and lead to an earlier onset of cancer

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ABSTRACT

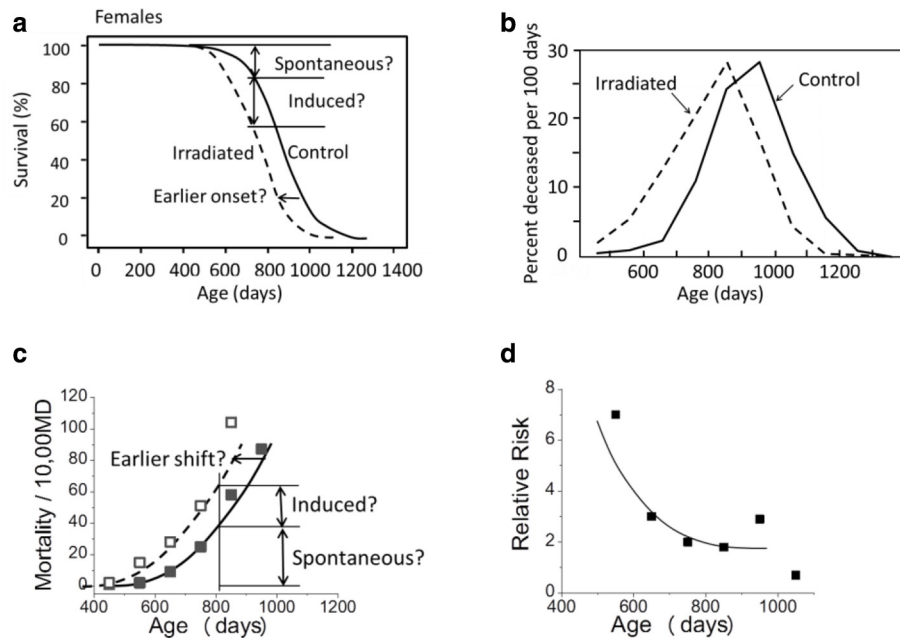
Cancer risks from radiation can be observed as an increase in mortality when compared to a control group. However, it is unknown if this increased risk results from the induction of cancer or from an earlier onset of cancer. In mouse studies, it has been repeatedly shown that after an irradiation, the survival curve is shifted toward lower ages, but remains parallel to the control curve, and the extent of the shift in time to lower ages is dose-dependent. This shift is not satisfactorily explained by the induction model which assumes that cancers in the exposed group consist of spontaneous and induced events. Consequently, it seems that this shift could be interpreted to mean that *all* animals in the exposed group had suffered from life shortening. Under this scenario, however, it turns out that the radiation effects can no longer be interpreted as the result of oncogenic mutations, because these effects would have to involve all tumors, and the effectiveness of radiation changes with the dose. This leads to the speculation that radiation exposures induce a broad range of tissue injuries, and that these injuries are subsequently subjected to longlasting systemic recovery processes which act as promoters for tumor cells. In other words, potential cancer stem cells which were located in the irradiated field can escape oncogenic damage but undergo stimulation later in life toward the development of malignancy from radiation-induced activated microenvironment. This is an unusual form of the non-targeted or bystander effects of radiation. It is worth noting that this model suggests that there could be a path or paths which could be used to intervene in the process of post-exposure carcinogenesis, and that cancer risks at low doses could be described as days or weeks of life lost.

INTRODUCTION

Radiation exposures are considered to be carcinogenic, but the underlying mechanisms which are involved are not well understood. Historically, the somatic mutation hypothesis has been discussed for many years, and it is successful in describing some types of radiation-related tumors in mice (*e.g.* Tsuruoka et al¹). However, for the majority of common types of cancers, the mechanism involved in their development is not understood. In the early phase of experimental studies using rodents, the possibility that a radiation exposure might give rise to an earlier onset of cancer (the earlier onset hypothesis or EOH) was raised.²⁻⁴ In those days, however, there was not yet sufficient human data concerning solid cancer risks, and, as a result, it was difficult to devise tests to determine which model fit human

data. Starting from around the 1990s, abundant data on human solid cancers started to accumulate, especially from atomic-bomb (A-bomb) survivors. Generally, the excess risks are expressed by the relative risk (RR) and excess absolute risks. Based on the survivor data and the somatic mutation hypothesis, Mendelsohn proposed that one step in a multistep carcinogenesis process might be omitted as the result of a radiation exposure. This could then give rise to the dose-dependent decrease in the slope of a log cancer rate *vs* log age relationship toward $n-1$ when n is the power for the corresponding background cancers.⁵ This shift, however, can be interpreted not only as an increased cancer rate but also as an earlier onset when compared to non-exposed controls. Regrettably, the proposal was not widely discussed among radiation scientists. In the present

Figure 1. Results from mouse experiments. The irradiated group represents B6C3F1 female mice exposed to chronic radiation for 400 days (total dose: 8 Gy). (a) Survival curve.⁶ (b) Deceased fraction resulting from all neoplasms.⁷ (c) Mortality calculated from the survival curve. The solid lines with solid squares (■) represent the control group, and the dashed lines with open squares (□) represent the exposed group. The dashed line represents a shift of the control curve toward a lower age by 100 days. (d) Temporal changes of the RR which were calculated from the ratio of the two mortality curves in C (see the Supplementary Material 1 for the derivation). RR, relative risk.



report, current arguments for the biological significance of the EOH model will be presented, along with comparisons of mouse experimental data to epidemiologic data from A-bomb survivors. These results indicate that a radiation exposure would not increase the risk of developing cancer through the induction of oncogenic mutations, but instead, through the activation of the surrounding stroma cells, which is an extreme form for a non-targeted or bystander effect of radiation.

The temporal changes in the RR are puzzling

It has been difficult for biologists to explain the decreasing trend in the RR with an increase in time since an exposure (Figure 1D). This is mainly because it is biologically counterintuitive to imagine that early onset cases (when the RR is higher) are more affected by the same dose of radiation when compared with late onset cases (when the RR is lower) since there are large but natural differences in individual lifespans. Intuitively, it would seem more likely that all cases are affected equally when the exposure doses are the same. This assumption is the foundation of this discussion of radiation injury models.

It is crucial to understand the epidemiological view of mouse data

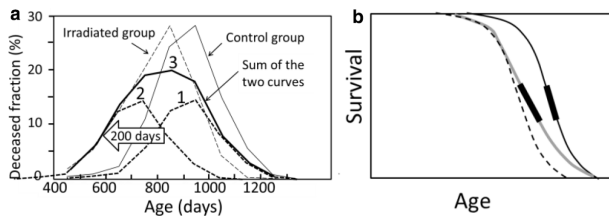
While experimental animals may not necessarily provide rigorous models for human carcinogenesis, robust comparisons were not sought out in the past. For example, in mice, it has been repeatedly shown that survival curves shift toward lower or younger ages following an exposure to radiation [e.g. Nowell and Cole; Tanaka et al^{6,8}], and this shifted curve often

appears to be exactly parallel to the control curve for non-irradiated animals. Figure 1 shows results from a large-scale study^{6,7}: there is a survival curve (Figure 1A); the temporal distribution of the deceased fraction (the number of mice which died from neoplasms in each 100 day observation window divided by the total number of mice in each group) (Figure 1B); and the mortality (or mortality rate: the number of mice which died in each observation window divided by the number of animals that were alive at the beginning of each window) calculated from the survival curve (Figure 1C). The ratio of the two mortality curves for the irradiated and control animals allows calculation of the RR values (Figure 1D). Note that biologists generally use the percent survivals and the deceased fraction (Figure 1A, B) to express the experimental results, whereas epidemiologists use cancer mortality and the RR (Figure 1C, D), and this can make discussions difficult between scientists in these different research fields.

Reasons why the EOH model is preferable to the somatic mutation hypothesis

Because the survival curve for irradiated animals shifts toward lower ages following a radiation exposure (Figure 1A), and remains parallel to the control curve, the pyramid shape of the deceased fraction in the irradiated group should also remain essentially the same as that of the control group, but is translated or shifted toward lower ages (Figure 1B). In the light of this observation, the question is whether or not the somatic mutation hypothesis can explain this parallel shift in the survival curve. Figure 2A shows a simulation result where 50% of the animals were randomly selected (curve 1) and assumed

Figure 2. (a) Results of a simulation experiment which assumed that a randomly selected 50% of the tumor deaths in the control group (curve 1) had occurred earlier than usual by 200 days (curve 2). The sum of the two curves (curve 3) represents the expected temporal changes in the deceased fraction. (b) Expected survival curve (the gray curve) derived from the curve 3 in Fig 2a. The solid line represents the control group and the broken line represents the irradiated group. The maximum slope of the survival curve is shown by the short bold line sections.



to have died earlier than usual by 200 days (curve 2). The sum of the two curves represents the expected results of the deceased fraction (curve 3). Because 50% of the deaths were shifted toward lower ages by 200 days, the initial portion of the synthetic survival curve (the center gray curve in Figure 2B) is in agreement with the observed curve (the broken line in Figure 2B). However, because the peak of the deceased fraction at ages 700–1000 days is flattened with this shift, the maximum slope at ages of 800–900 days in the synthetic survival curve is reduced and becomes shallower. Finally, because it was assumed that 50% of the animals remain unaffected, the ages at which individuals in the control and the irradiated populations all die remain close to each other. In short, the observed parallel shift in the survival curve cannot be accomplished by randomly selecting a fraction of the animals in the control group and letting them die earlier than usual. This leads to the speculation that the parallel shift in Figure 1 could indicate that *all* individuals in the irradiated group were affected and died earlier than usual by about 100 days.

Another reason to support the EOH model is that the declining pattern of the RR value can be seen as an inevitable consequence of this model. Specifically, the age-related mortality is expressed as an exponential function such as $f(x) = ax^5$ where $f(x)$ represents the mortality, x is the age, and a is a constant. Next, mortality with an earlier onset of b years can be described as $f(x) = a(x + b)^5$. Because the RR is the ratio of mortality between the two groups, the RR at age τ is expressed as $a(\tau + b)^5 / a\tau^5 = 1 + 5b\tau^{-1} + 10b^2\tau^{-2} + 10b^3\tau^{-3} + 5b^4\tau^{-4} + b^5\tau^{-5}$, which is a monotonously decreasing function.

It should be noted here that the EOH model can be valid for common cancers where the background rate increases exponentially with aging. This is because if the age-related incidence or mortality for a specific type(s) of cancer levels off after some age, then an earlier shift of the onset age would not always cause an increased risk of cancer. This implies that the EOH model would not apply to leukemia or possibly to thyroid cancers in humans.

Interpretation of A-bomb survivor data using the EOH model

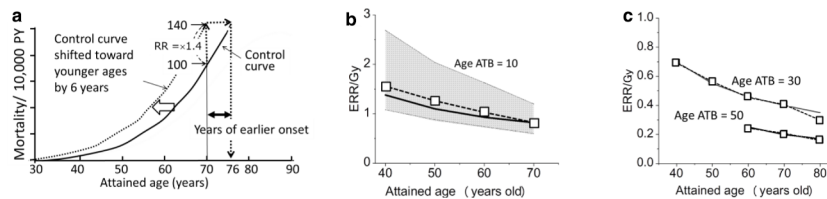
Since the EOH model appears to be reasonable based on animal data, an attempt was made to calculate the number of years of life lost due to an earlier death from cancer in A-bomb survivors. Figure 3A shows a simple description of the approach. Specifically, assume that in this control population the baseline mortality at 70 years of age is 100 per 100,000 person-years (PY), and the RR for those who were exposed to 1 Gy (RR_{1Gy}) is 1.4. The mortality of the irradiated group is then calculated as 140 per 100,000 PY (the baseline mortality \times RR). Finally, we can examine the age of the control group at which the mortality value reaches this same value of 140 per 100,000 PY. From Figure 3A, this is 76 years for the control group. Consequently, the exposed group appears to have experienced a 6 year shift towards an earlier mortality. In this way, the number of years lost by earlier deaths from cancer following an exposure to 1 Gy was estimated, and the summary is shown in Table 1 along with the corresponding RR values for a comparison (see the Supplementary Material 1 for the derivation). It should be noted here that the two different expressions for cancer risk; *i.e.* the RR value and the number of years lost, are equally valid because they explain the risks of cancer mortality in both the vertical and horizontal directions in the figure.

Furthermore, by calculating the ratios of the values of the shifted to non-shifted mortality curves, the RR value at various attained ages can be calculated. The predicted temporal pattern of the excess RR (ERR) and the reported values are compared in Figure 3B (where the survivor's age at the time of exposure to the bomb, or age ATB, was 10 years) and Figure 3C (where the age ATB was 30 or 50 years). It is striking to see that the observed and the predicted curves are in close agreement. This means that the temporal changes observed are predictable by assuming a single fixed parameter (*i.e.* the number of years to an earlier death) for each age-ATB group, which in turn indicates that the length of time that death was advanced by an irradiation remains essentially constant throughout one's life while the ERR changes with attained age.

The EOH model and the somatic mutation hypothesis are not compatible

The somatic mutation hypothesis assumes that the frequency of the mutations increases with an increase in the dose, and hence the number of unfortunate excess cases is assumed to increase with an increase in the dose. Thus, a linear dose response sounds reasonable (Figure 4 upper panels). However, this assumes that a small number of affected cases exists among many unaffected individuals, and this cannot properly explain the mouse survival data in which the entire survival curves are shifted or translated toward younger ages after irradiation, and remain parallel to the control curves (Figure 1A). On the other hand, if we assume that *all* tumor deaths were affected by the exposure to radiation (Figure 4 lower panels), the shift of the mouse survival curve can be readily explained, but now the somatic mutation hypothesis would not apply. This is because with the mutation induction scenario, one is forced to assume that the target gene has to vary at different dose levels because at low doses the effect on mutations is weak (there is only a small shift in the mortality curve),

Figure 3. (a) A schematic drawing illustrating how to estimate the number of years for earlier deaths from cancer. Panels (b, c) show the observed (solid line) and simulated (\square) temporal patterns of the ERR with aging (⁹ and present results). The shaded area in Fig. 3B indicates the 95% confidence intervals associated with the estimated age-ATB dependent change of the RR (Table 4 from⁹).



whereas at higher doses the effect is stronger (there is a larger shift in the mortality curve), and this is unlikely. If somatic mutations cannot explain this shift in the survival curve, then what mechanism might be involved? One possibility is the presence of natural or normal processes involved in the recovery from tissue injuries.

Evidence indicates that there is a close association between the carcinogenic effects of radiation and the processes involved in recovery from radiation injuries in the stroma

There are a number of reports describing radiation responses in normal tissues, and examining interactions between stroma and cancer cells. Below is a categorical list of examples which appear to support the EOH model rather than the theory of somatic mutation induction.

- (1) Cancer cells can grow more robustly when transplanted into pre-irradiated normal tissues of the animals [e.g. Withers and Milas¹⁰; Lee et al¹¹].
- (2) An irradiated or *N*-nitrosomethylurea (MNU) treated microenvironment can stimulate untreated non-tumorigenic or normal cells to transform into malignant phenotypes [e.g. Nguyen et al.¹²; Dührsen and Metcalfe¹³; and Maffini et al¹⁴].
- (3) The formation of malignant foci *in vitro* or of tumors *in vivo* following an injection of carcinogen-treated cells is often suppressed by the presence of co-administered non-transformed cells [e.g. Kamiya et al¹⁵; Watanabe et al¹⁶; Chan and Neel¹⁷].
- (4) Tumor formation requires not only transformed cells, but also an abnormal microenvironment [e.g. Bissell and Hines¹⁸].

- (5) Altered expression of various cytokines in a normal tissue persists for many months after an irradiation in mice [e.g. Rubin et al¹⁹].
- (6) The frequency of radiation-induced transformation in C3H 10T1/2 cells *in vitro* increases with an increase in the radiation dose, while it is independent of the number of cells seeded per dish. These results indicate that irradiation induces some common events (quantitatively reproducible by irradiating only 200 cells) followed by rare events during focus formation.²⁰ This observation is now understandable if irradiation induces robust cellular damage which subsequently leads to recovery-related secretions of signaling molecules such as transforming growth factor β (TGF β).

A new model of radiation carcinogenesis

If we adopt the EOH model, and assume that all individuals who developed cancer are affected by an exposure, it seems likely that the initial events leading to the development of cancer following a radiation exposure would not be the induction of an oncogenic mutation in a stem cell which was located in the radiation field, but rather more robust injuries in tissue micro-environments; e.g. insults to normal tissues followed by recovery processes which can lead to the development of potentially abnormal conditions in the microenvironment; e.g. longlasting inflammation (“inflammation without infection”) or stromal activation (Figure 5). This concept is similar to the bystander or non-targeted effect of radiation, except that stem cells which may potentially become malignant later in life are located within the irradiated field, but are free from oncogenic insults. The simplest mechanism involved in the initial phase can be the production of DNA double-strand breaks (DSBs) which occur in all irradiated cells (about 40 DSBs are induced per cell with an irradiation

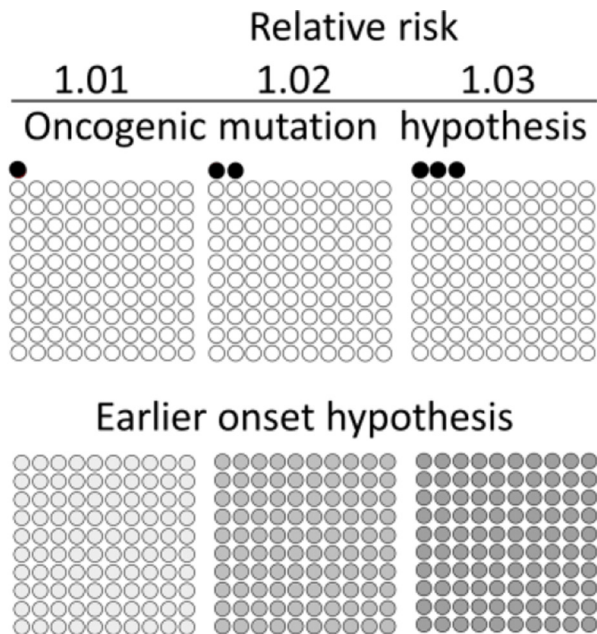
Table 1. Comparisons of estimated RR at an attained age of 70 years vs estimated years of life lost by cancer deaths in A-bomb survivors following exposure to 1Gy

Age at exposure (years)	RR _{1Gy} at an attained age of 70 years ^a			Years of life lost after exposure to 1 Gy		
	Males	Females	Mean	Males	Females	Mean
10	1.5	2.1	1.8	7	14	10
30	1.3	1.6	1.4	4	8	6
50	1.1	1.3	1.2	2	4	3

RR, relative risk.

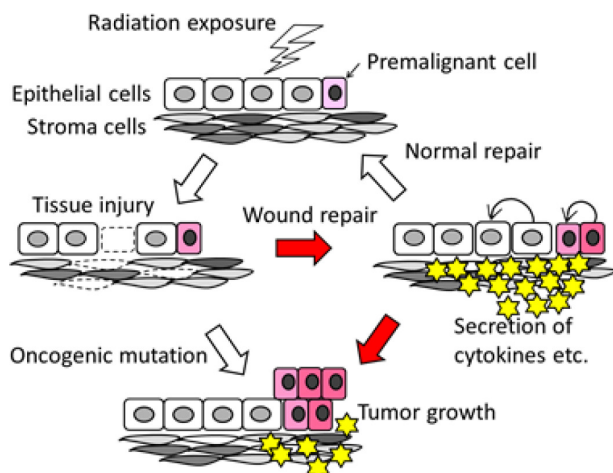
^aOzasa et al.⁹

Figure 4. Two alternative models to explain the carcinogenic effect of radiation. The upper panels present a schematic expression of the somatic mutation hypothesis. ○ indicates spontaneous cancers and ● indicates radiation-related excess cancers. The lower panels represent a schema for the EOH model. The darker colors represent stronger life shortening effects.



of 1 Gy). Because the number of DSBs should be linearly related to the dose, the present model fits with the linear dose response observed in mice (*i.e.* there is a linear correlation between the

Figure 5. A schematic drawing illustrating the two models of radiation carcinogenesis. The somatic mutation hypothesis assumes that radiation exposure may add one mutation in epithelial stem cells and thereby increasing the risk of developing cancer. In contrast, the EOH model assumes that DNA damage to the microenvironment in normal tissues may lead to an altered microenvironment which acts to produce conditions favorable for tumor cell growth through the secretion of various signaling factors (solid arrows).



shortened life span and the radiation dose.^{3,21,22} Subsequently, the stalling of replication forks,²³ DNA damage-induced cell cycle arrests,²⁴ cell death-induced activation of macrophages,²⁵ cytoplasmic DNA (micronucleus)-derived activation of cyclic GMP-AMP (cGAS) synthetase²⁶ etc. may lead to longlasting inflammatory responses,^{27,28} and to the secretion of signaling molecules which can act to promote tumor cells.

DISCUSSION

Which is more critical: somatic mutations or inflammatory responses?

It seems clear that the parallel shift of the mouse survival curve toward lower ages after irradiation cannot be satisfactorily explained by the mutation induction model of cancer. On the other hand, there are examples which fit the mutation induction model; *e.g.* tumors which developed after irradiation in mice that are heterozygous for genes related to carcinogenesis bear deletions in a wild-type allele.^{1,29,30} Therefore, there seems to be at least two types of malignancies: one type is composed of common types of cancers which develop predominantly late in life and fit the EOH model, and the other type consists of those which develop early in life (but with a low incidence) and do not fit the EOH model (probably leukemia and thyroid cancers).

Issues of cancer risks at low doses and low dose rates

There have long been arguments concerning cancer risks at low doses that cannot be measured epidemiologically or experimentally. The presence or absence of a threshold dose has been and still is being argued, for example. Under the present EOH model, although there is still room for arguing that there is a threshold dose, a clear shift in our way of thinking about cancer risks at low doses is obvious. For example, under the assumption of a linear non-threshold response, a single exposure to 20 mGy (the annual dose limit for radiation workers and those who reside in the contaminated area which resulted from the nuclear power plant accident in Fukushima) gives an estimated RR of around 1.01 for cancer death which is equivalent to a life shortening of 2–14 weeks depending on the gender and the age ATB (read the number of years in Table 1 as weeks because 20 mGy is 1/50 of 1 Gy, and 1 week is about 1/50 of 1 year). Following this line of argument, it seems likely that at low doses where the effect on cell killing (another important action which may cause late effects) is likely to be negligible, cancers which arise among radiation-exposed individuals are likely to be totally spontaneous in origin but were stimulated to emerge slightly earlier than usual. Concerning the dose–rate effect of low-LET radiation, the model would concern itself with what might be described biologically as a balance between the induction of tissue injuries (stromal activation) and the subsequent recovery apart from physical descriptions of the track structure of charged particles; *i.e.* the linear quadratic model.

Why not intervene during radiation carcinogenesis
Since the somatic mutation hypothesis assumes that an irradiation can instantaneously induce critical mutations involved in a multistep carcinogenesis process, there seems to be no way to erase or reverse the effect of a radiation exposure (*i.e.*

radiation-induced initiation events persist for a long period of time^{31,32}). However, if radiation carcinogenesis proceeds through the hosts' recovery processes from damage in normal tissues, there could be a possibility in the future that it might be possible to develop methods to mitigate radiation-induced carcinogenesis processes.³³ Specific approaches toward this goal may include, for example, controls on the expression of cGAS,²⁶ GPCR (G protein-coupled receptor),³⁴ MK2,³⁵ CD28,³⁶ PUFA (n-3 polyunsaturated fatty acids),³⁷ TGF β and PDGF³⁸ etc, and in turn, this may be applicable to the processes involved in spontaneous carcinogenesis. It has been reported that the use of, for example, non-steroid anti-inflammatory drugs^{39,40} or soy isoflavones,⁴¹ might help prevent radiation carcinogenesis, although actual experimental data are still limited.

Future tasks: expanding collaborations between researchers in different fields

The EOH model suggests that it would be more crucial than ever for researchers in diverse research areas (e.g. radiation biologists, oncologists, radiologists, epidemiologists, nutritionists, pharmacologists, immunologists etc.) to communicate, share their common interests, and develop collaborative efforts to

understand the mechanisms involved in radiation carcinogenesis and its prevention. Such efforts will hopefully lead to the development of concepts that could help prevent or block general carcinogenic processes, and thereby contribute to world health.

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