The influence of cell context on the selection pressure for p53 mutation in human cancer

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Although p53 mutation is, overall, by far the most frequent somatic genetic abnormality in human cancer, in some common tumour types, notably carcinoma of breast, it is seen only in a phenotypically-distinct sub-set of cases, often correlated with adverse prognosis. Conventionally, this is viewed as the consequence of random differences in acquired genetic events acting on a common cell. Here we develop a fundamentally different hypothesis, which proposes that the liability of a given tumour to exhibit p53 mutation is predetermined by the nature of its cell of origin and, more specifically, depends on the extent to which wild-type p53 forms a rate-limiting step in the control of proliferative lifespan in that cell. In other words, the phenotype of the cell of origin constrains both tumour phenotype and ‘choice’ of genetic events. This concept can be extended to tumour progression, where evidence particularly from thyroid tumorigenesis suggests that a switch in differentiation state can play a major causal role in tumour evolution by altering the selection pressure for p53 mutation. Finally, analysis of transformed thyroid cells has also revealed a novel physiological mechanism by which growth suppression by wild-type p53 may be evaded in cell types whose lifespan control is p53-independent.

Introduction

Early surveys of the structure and expression of the tumour suppressor gene p53 suggested that inactivating mutations might be a common denominator in the vast majority of human cancers. Indeed, it was initially suggested that p53 mutation (or the associated elevation of cellular p53 protein levels) might even be a molecular diagnostic marker of the malignant state per se (1). Subsequent analyses of large series of individual tumour types have, however, revealed a much more complex story.

First, it is now clear that some (albeit rare) cancers uniformly show very low rates of mutation. Many of these are biologically ‘unusual’ tumours, for example germ cell and embryonic cancers (2–5), for which explanations based on atypical features such as telomere dynamics (6) are not hard to envisage. Others use indirect means to achieve a ‘p53-null’ state, notably gene amplification and hence over-expression of the functional inhibitor mdm-2, which is seen for example in many sarcomas (7,8).

What is more difficult to explain is the finding that in some common epithelial cancer types, invasive ductal carcinoma of breast being perhaps the best example, p53 mutation is often observed, but only in a sub-set of cases [in breast variously estimated as between 15 and 35% (9)]. Furthermore, there is now a consensus that these mutant p53 (mp53) cases have a significantly poorer prognosis, giving them a clinical as well as biological interest.

To date, the existence of such an mp53 sub-group has been explained conventionally on the ‘play of chance’, i.e. that these are cancers that just happened to acquire a p53 mutation, whereupon the resulting sub-clone gained a persistent growth advantage. This could be direct, either through a reduced liability to growth inhibition, or cell death in response to endogenous (still poorly defined) or exogenous (therapy-related) DNA damaging agents. Alternatively it could be indirect (delayed), through the potential mutator effect of losing normal p53 function. Although support for some of these possibilities can be found from in vitro (10,11) and xenograft experiments (12), as emphasized in a recent review (13) it is still unclear to what extent they are significant in the context of real human cancers in vivo.

Here we develop a fundamentally different hypothesis, which proposes that the liability of a given tumour to exhibit p53 mutation (i.e. the selection pressure for mutation) is predetermined by the nature of its cell of origin and, more specifically, depends on the extent to which wild-type (wt*) p53 forms a rate-limiting step in the control of proliferative lifespan in that cell. Drawing together several previously unrelated areas of breast cancer research, together with our own studies of thyroid tumorigenesis, we present evidence that the significance of this lifespan-regulatory role of p53 varies dramatically between epithelial cells of the same ‘lineage’, depending on their initial differentiation state. The existence of phenotypically distinct mutant or wild-type p53 sub-groups within a given cancer type can therefore be re-interpreted as the result, not of random differences in acquired genetic events acting on a common cell, but rather of an underlying difference in the phenotype of the cell of origin, which subsequently constrains both the tumour phenotype and the ‘choice’ of somatic genetic events.

Evidence from breast cancer

Clinical observations

The continuing need for a prognostic marker to inform therapeutic decisions in breast cancer, together with the fortuitous stabilization of many mutant p53 proteins, has generated a plethora of immunocytochemical studies of p53 in this disease (reviewed in 14). While the majority of such surveys concluded that p53 over-expression was an independent prognostic marker, interpretation was clouded by the subsequent realization that only a sub-set of such positive cases actually harbour a mutant gene, the proportion depending critically on the operational cut-off used for defining positivity (9,13,15–17). (The biological significance of the stabilization seen in non-mutant cases is discussed below).

*Abbreviations: wt, wild-type; OR, oestrogen receptor; EGFR, EGF receptor; HPV, human papillomavirus; p.d., population doublings; CK, cell cytokeratins.
Later studies (15,18–24), using direct sequence analysis, although inevitably fewer in number, have now provided a more objective basis for genotype/phenotype correlation. The consensus remains that \( p53 \) mutation (found in 20–25% of cases in most series) correlates with poor prognosis, as measured either by relapse-free or overall survival, even when other conventional factors such as age and lymph node status are taken into account. Multivariate analysis frequently singles out \( p53 \) mutation as an independent prognostic marker comparable in predictive power to ‘stage-related’ factors such as node status, and superior to many other biological markers including steroid receptor expression (13). In some series this effect persists even when patients are stratified by lymph node status (23,24). In most studies, the relative risk (for recurrence or death) attributable to \( p53 \) mutation appears to be in the order of 2- to 4-fold, although there are inevitably variations related to differences in methodology and/or patient selection (13).

\( p53 \) mutation correlates well with other established negative biological prognostic markers, including high histological grade, high S-phase fraction, EGFR receptor (EGFR) expression, and absence of oestrogen receptor (OR), although none of these associations is absolute (see below).

A separate set of studies (25–27) has also led to the definition of a sub-set of poor prognosis breast cancers (again representing 20–30% in most series), this time on the basis of intermediate filament expression patterns. These are characterized by expression, not only of the luminal breast cell cytokeratins (CKs)8 and 18, but also of markers normally associated with basal (myoepithelial) cells, i.e. CK14 and vimentin, and like basal cells they express high levels of EGFR and are OR-negative. This contrasts to the majority of breast cancers which express a pure ‘luminal’ pattern of cytokeratins, i.e. CK8 and 18 (with or without CK19), low EGFR levels and are often, but not always, OR-positive (27) [the latter variability probably reflecting the known occurrence of both OR-positive and -negative cells in the normal luminal population (28)].

Although unfortunately, as far as we are aware, no study has directly compared \( p53 \) gene sequence with these phenotypic markers in the same cases, taken together, the data clearly suggest that both sets of studies have identified the same poor prognosis subgroup, characterized by an intermediate ‘basal/luminal’ phenotype (positive for CK8, 18 and 14, vimentin, EGFR; negative for OR), high growth fraction, and \( p53 \) mutation. The imperfect correlation observed between OR-negativity and \( p53 \) mutation can be readily explained by the observation (26) that OR-negative tumours can belong to either the intermediate ‘basal/luminal’ or the ‘luminal’ subgroups.

**Cell biological studies**

The majority of normal breast epithelial cells present in the intact gland and (depending on the medium) in early-passage mammo-plasty cultures, fall into two categories: (i) basal (or myoepithelial) cells characterized by expression of CK5 and 14 and vimentin, and (ii) luminal cells expressing CK8, 18 ± 19, but not vimentin (29–31). However, a population of so-called ‘post-selection’ cells grows out of mammo-plasty cultures (in defined media such as MCDB 170), after the majority of early-passage cells have senesced (29,30) which shows an ‘intermediate’ pattern (positive for CK8, 18 and 14, vimentin and EGFR; negative for OR) that is strikingly similar to the phenotype described above in \( p53 \) mutant cancers. The high proliferative capacity of these cells together with this ‘uncommitted’ differentiation state has led many observers to regard them as derived from a small ‘stem-cell’ pool present in the basal layer of the normal gland (29,30).

These cells, which are often loosely referred to as ‘HMEC’, have become the focus of several studies on the regulation of mammalian cell senescence. Their striking feature, first observed by Band and colleagues (32), is that in contrast to most mammalian cells they can be efficiently immortalized by the human papillomavirus (HPV) E6 gene acting alone, without the need for HPV E7. The primary effect of E6 is to extend the proliferative lifespan of HMEC by up to 20 p.d. (33), which overcomes senescence and places them in a state (M2 or ‘crisis’) from which they are able to undergo true immortalization through an additional stochastic event(s) associated with telomere stabilization (33). As expected, the essential function of E6 in this system is to abrogate wt \( p53 \) function, as shown by the ineffectiveness of E6 mutants that do not target \( p53 \) (34), and by the ability of some (although not all) mutant \( p53 \) genes to reproduce the effect of E6 (35,36).

This behaviour is in marked contrast to that of other epithelial cell populations present in the mammary gland. Two groups (37,38) have for example demonstrated the existence of an epithelial cell type in early passage mammo-plasty cultures, which shows the exact opposite pattern from that of the post-selection HMEC, i.e. extension of lifespan and immortalization by HPV E7 alone without any requirement for E6. Unfortunately, the exact nature of the cells involved was not clear from these studies, although from the known composition of early passage cultures it is likely to be a more differentiated cell type (probably of basal phenotype). Furthermore, in a more defined culture system (from milk), cells with luminal differentiation (corresponding to the majority phenotype found in breast cancer) were also shown not to be susceptible to immortalization by E6 alone, but underwent a major extension of lifespan in response to E7 (from 20–30 to 60–100 p.d.) (37,39). In this case, though, eventual escape from mortality did appear to require the additional action of E6.

Such data clearly point to the existence of epithelial sub-populations within the breast with major differences in their response to tumour-suppressor gene inactivation. It already seems clear that there is a ‘stem’ type cell whose proliferative lifespan is regulated by a \( p53 \)-dependent pathway and can escape senescence without the need to abrogate the Rb-dependent pathway (on the assumption that this is the critical target for HPV E7). Conversely, in more differentiated cells, including the important luminal type, the Rb-dependent pathway appears to be rate-limiting for extension of normal lifespan, with a variable additional requirement for abrogation of \( p53 \) to achieve true immortalization.

**Unifying hypothesis: differential control of proliferative lifespan dictates differential selection for \( p53 \) mutation**

Combining the data from cell biological and clinical studies, one obvious explanation emerges for the existence of subsets of invasive ductal breast cancer, namely that they are derived from subpopulations of normal breast cells having different rate-limiting controls on proliferative lifespan. Thus the minority subset having a high frequency of \( p53 \) mutation would be predicted to arise from the ‘stem’ cell population in which \( p53 \) is the rate-limiting control and which share with the \( p53 \) mutant cancers the same pattern of cytokeratin, vimentin, EGFR and OR expression. Conversely, the majority group, with wild-type \( p53 \), would be expected to arise (as is indeed already widely accepted) from cells with a luminal
phenotype. Although the lifespan regulation of luminal cells is less well-defined, it is reasonably clear that, in contrast to ‘stem’ cells, the Rb pathway is a major rate-limiting control. Indeed, the magnitude of lifespan extension inducible by HPV E7 (without the addition of E6) in vitro (37,39) is consistent with such cells being able to generate a lethal tumour burden before ever reaching the population doubling level at which wt p53 would represent a significant ‘hurdle’, thus accounting for the lack of selection pressure for p53 mutation.

As illustrated in Figure 1, this idea leads to an entirely different view of the relationship between tumour phenotype and its underlying genotype. Most reviews of this field (see for example 13,40) make the tacit assumption that the existence of a more aggressive subset within a given cancer type is somehow driven by these cases having acquired a p53 mutation, i.e. that different phenotypes arise from a common cell of origin dependent on the chance nature of the genetic events undergone (Figure 1a). If our interpretation is correct, however, both the genotype and the phenotype of the tumour are essentially predetermined by the phenotype of the cell of origin (Figure 1b). Viewed in this way it is not that the tumour is aggressive and less differentiated because it has acquired a p53 mutation but that the p53 mutation is simply an inevitable reflection of the normal controls operating in the cell of origin. In other words the differences in tumour phenotype may be determined more by the properties of their cell of origin than by the nature of the mutational events which they undergo. Of course, this does not exclude additional secondary consequences arising from p53 mutation leading, for example, to genomic instability that may make a contribution to the eventual tumour phenotype, but it makes the relationship between genotype and phenotype much less direct.

Support from other tumour types: thyroid cancer

The existence of subpopulations with differential lifespan regulation is also well-demonstrated by our studies of human thyroid epithelial cells (41–43). Here the majority phenotype, both in the gland in vivo and in early passage primary cultures, is the follicular cell that forms a tight ‘cobblestone-pattern’ monolayer that is typical of well-differentiated epithelium and expresses the expected pattern of simple epithelial keratins CK8 and 18, together with abundant plasma membrane E-cadherin (43). The proliferative lifespan of these cells is extremely limited, both in vivo and in vitro (41,42), growth arrest (M2 in Figure 3) being primarily mediated by a pathway that can be abrogated by HPV E7 (44, J.Bond et al., unpublished) and hence presumably involves pRb (as in early passage and milk-derived mammary cells). Abrogation of wt p53 function (by HPV E6 or a dominant-negative p53 mutant) is without effect on this initial proliferation block (42,44, J.Bond et al., unpublished). Although loss of Rb function extends the lifespan of these thyroid cells by around 15–20 p.d. (44), it is, however, insufficient for complete escape from senescence, a second arrest supervening that is also independent of wt p53 function and is mediated by still unknown mechanisms (Figures 2 and 3).

The lack of involvement of p53 at any stage in the regulation of lifespan in thyroid follicular cells in culture provides therefore a very plausible explanation for the striking absence of p53 mutation in the corresponding cancers in vivo (differentiated follicular cell carcinomas) (45). Equally, the key role of Rb is consistent with increasing evidence for abrogation of this pathway in these tumours by loss of the cyclin-dependent kinase inhibitor p16INK4a (46; M.Ivan, unpublished).

Although not recognized for many years, a second minor
subpopulation of epithelial cells is present in primary cultures of normal human thyroid at a frequency estimated at $<1:10\,000$ (43). These cells are clearly of follicular origin since many initially express the follicular cell-specific secretory product thyroglobulin and they all retain expression of the thyroid transcription factor PAX8. Unlike the classic follicular cell, however, they show a mesenchymal-like morphology, grow in a dissociated pattern and lack E-cadherin expression. Curiously, they exhibit a diminution in immunostainable CK8 but a dissociated pattern and lack E-cadherin expression. Curiously, they exhibit a diminution in immunostainable CK8 but

**Tumour progression: A switch of cellular context**

If the phenotype of the cell of origin can have such a determining influence on the sequence of somatic mutations in a given tumour type it is reasonable to ask whether a switch in phenotype could change the course of tumour evolution. Major switches in differentiation programme are, of course, commonplace in tumours and have long been described by pathologists in terms such as metaplasia, trans-differentiation, de-differentiation, etc. What has not been so generally appreciated, however, is the fundamental effect that such an epigenetically driven process could have on the selection pressure for genetic abnormalities. Work from our laboratory has provided strong evidence that this type of mechanism can indeed be a major component of human cancer progression.

In an *in vitro* model of clonal progression in thyroid tumorigenesis (41,44), we have observed that follicular cells that have escaped the initial Rb-regulated lifespan checkpoint (M0 in Figure 3) by expression of SV40 T (as opposed to HPV E7) undergo two mutually-exclusive fates. They either (i) remain well-differentiated, in which case they undergo irreversible growth arrest after 15–20 p.d., as in E7-expressing cells (M1 in Figure 3); or (ii) spontaneously develop poorly-differentiated subclones that exhibit a greatly extended proliferative lifespan (by up to 50 p.d.). The correlation between de-differentiation and extension of lifespan is absolute, suggesting that it is not just a passive epiphenomenon but is causally linked to the change in growth control. The frequency of this event, estimated at greater than 1 per 3000 cell divisions, is much higher than that expected from somatic mutation (although we cannot of course exclude the possibility that mutation in any one of several alternative genes might generate the same phenotypic change). Furthermore, the loss of differentiated features is identical to that which characterizes the spontaneously arising pseudo-mesenchymal variant cells (referred to above) in normal thyroid cultures (43), and for which there is no reason to suspect a mutational basis. Taken together, this suggests that the thyrocyte is liable, with a given probability, to undergo a spontaneous switch in differentiation programme the result of which is (i) to extinguish most of its thyroid-specific characteristics, and (ii) to effectively convert its proliferative behaviour to that of a mesenchymal cell (Figure 3).

Such epithelial–mesenchymal transitions have been well documented in other tumour progression models, and indeed in normal development (50–53), but have not hitherto been related to proliferative lifespan controls. Our results lead to a model (Figure 3) in which escape from the otherwise insurmountable M1 checkpoint is achieved not by directly overcoming it, but by a side-step in which it is substituted by a new checkpoint (effectively that of a fibroblast) that can now be overcome provided that the function of the p53 as well as the Rb pathway is abrogated. This is consistent with the failure of cells expressing E7 (only Rb inactivated) to undergo this escape process (44). These data therefore go further than those of Band and co-workers (37,39) in that they not only describe two distinct ‘tracks’ for proliferative ageing in different subpopulations of epithelial cell, but also suggest that it is possible for a cell to switch from one to the other.

Loss of differentiation is a widespread feature of tumour progression and frequently accompanies more aggressive behaviour. The thyroid provides a particularly clear-cut example of the abrupt phenotypic switch that occasionally occurs from the common well-differentiated papillary cancer with limited proliferative potential and excellent prognosis, to the exceptionally aggressive undifferentiated (anaplastic) form (54). Conventionally, such changes in tumour differentiation,
while useful for diagnosis, have tended to be regarded as epiphenomena, secondary to the underlying mutational-driven progression of tumour growth. The parallels between our in vitro model and the conversion of well- to undifferentiated thyroid cancer in vivo suggest, however, that at least in this example of progression, increased proliferative potential may be dependent on epigenetic as well as mutational mechanisms. We speculate that progression in vivo results from a synergism between the differentiation switch discussed here and the occurrence of the p53 mutation, which is a hallmark of undifferentiated thyroid cancers (45). The rarity with which the transition to undifferentiated cancer is seen clinically in thyroid can be explained by the need for the differentiation switch and the p53 mutation to arise independently in the same cell before any selective advantage is obtained.

Although less clear-cut, there is much indirect evidence to suggest that a similar epigenetic mechanism may be important in the progression of breast cancer to hormone (oestrogen) insensitivity. The assumption in this field has usually been that loss of endocrine response results through the acquisition of some additional mutation. However, there are several examples from in vitro models in which such a change of phenotype clearly occurs as the result of an epigenetic switch, in one case (55) being induced by a simple change of medium constitution, and in another (56) by altering DNA methylation status with azacytidine. These changes are accompanied by a variable acquisition of other phenotypic markers associated with the ‘stem cell’ phenotype referred to above, including down-regulation of OR expression and increased expression of EGFR and vimentin. Unfortunately, though, because these studies have been performed using cell lines, they are not informative as regards changes in proliferative lifespan regulation.

Cell-type specificity in lifespan regulation: Underlying mechanisms

The basis for the differential utilization of p53-dependent and -independent growth inhibitory pathways in control of cellular senescence is still unknown, perhaps not surprisingly since the fundamental molecular links between proliferative ageing and cell-cycle inhibition are themselves far from clear. In the case of p53 there is at least a plausible mechanism based on the use of telomere erosion as a ‘clock’, the activation of p53 occurring in response to a ‘DNA damage’ signal that is generated when one or more telomeres has shortened to a critical threshold (47,57,58). Even this, however, is unproven, and for p53-independent senescence the link between population doublings and induction of growth inhibitors such as p16ink4a is even less clear. Nevertheless, it is useful to consider several general mechanisms by which cells that use a p53-independent lifespan control, e.g. thyroid follicular and early passage breast cells, succeed in evading (or at least postponing) senescence-related growth suppression by wild-type p53.

1. ‘Stopping the clock’. According to this model a potential p53-dependent lifespan checkpoint does exist, but before it is reached, the lifespan ‘clock’ (e.g. telomere erosion) is effectively stopped (58). This might be predicted where, as in the case of thyroid follicular cells, there is an ‘early’ lifespan checkpoint (M1 in Figure 3), which appears to be very difficult to overcome by somatic mutation (perhaps because it is maintained by multiple redundant pathways).

2. ‘Uncoupling the clock’. A second possibility is that some cell types may constitutively lack the molecular link(s) between telomere erosion (or other lifespan clocks) and activation of the p53 pathway. This could correspond to the observation in mouse models of major tissue-specific variations in the stabilization and/or activation of wt p53 in response to exogenously-induced DNA damage (whole body irradiation) (59,60).

3. ‘Inhibiting the response’. Finally, although senescence activates wt p53, the biological response may be prevented (or at least obviated) by a cell-type dependent inhibitory mechanism. Strong support for this idea has recently been provided by our investigation into the tolerance of wt p53 by transformed rat thyroid epithelial cells (61,62).

These immortal cells demonstrate elevation of nuclear wild-type p53 protein content with a characteristic cell–cell heterogeneity. This phenotype is also now well recognized in many human cancers expressing wild-type p53 such as breast (14,16), and intriguingly is also induced by expression of HPV E7 in early passage breast (38) and thyroid follicular cells (J.Bond, unpublished). This p53 protein stabilization indicates that the p53 pathway is being activated, but that there is apparently a resistance to its growth inhibitory/apoptotic effect. In our rat thyroid cell line model, we have confirmed, using reporter constructs and EMSA assay, that the increase in p53 protein content is indeed not accompanied by a corresponding increase in its transactivation or DNA binding activities (62).

The most obvious inhibitor is the MDM2 protein (7), which blocks transactivation by p53 through a specific interaction with its N-terminus (63) and overexpression of MDM2, consequent upon gene amplification is, of course, a recognized mechanism for tolerance of wt p53 in some tumour types, mainly sarcomas (8). In our transformed thyroid cells however, we have observed very high levels of MDM2 expression compared with untransformed controls, in the absence of amplification (62). Furthermore, although still limited in scope, several clinical surveys point to a similar phenotype. For example, increased mdm2 expression was observed in thyroid cancers with wt p53 (64), and intriguingly in breast cancers elevated expression correlated with OR positivity (65–67), just as would be predicted if this is a feature of luminal cell differentiation. At least in transformed thyroid cells, such elevation of MDM2 expression appears to be dependent on wild type p53, since it is abolished by expression of a dominant negative mutant (62). Finally, the importance of mdm2 for the ‘resistance’ of these cells to wt p53 was shown directly by micro-injection of an antibody, 3G5, which blocks MDM2–p53 interaction. This strikingly relieved the inhibition of p53 function, leading to an increase in its transactivation activity and, depending on the model, to apoptosis or growth arrest (62, J.P.Blaydes, unpublished).

These data can all be resolved if one proposes that the MDM2 promoter in cell types such as thyroid (and possibly breast luminal) epithelium is unusually sensitive to stimulation by p53, such that activation of wt p53 (e.g. by proliferative...
ageing and/or de-regulation of cell-cycle control) generates an MDM2 feed-back response (7) of sufficient magnitude to keep the level of unbound, active p53 below that required for triggering other biological responses, such as growth arrest or apoptosis. This is supported in our model by the absence of an elevated level of other (non-MDM2) transcriptional targets such as p21WAF1 (62). In this way, in such cells (provided other an elevated level of other (non-MDM2) transcriptional targets triggering other biological responses, such as growth arrest or p53 MDM2 feed-back loop.

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Why some cell types should choose to down-regulate their responsiveness to p53 in this way is unclear. It may, however, relate to a need to avoid a high rate of apoptosis from activation of p53 (by endogenously generated DNA damage) throughout life in epithelia such as thyroid, which have a very limited self-renewing potential. This may be particularly important in tissues that have an unusually high exposure to such damaging agents. Thyroid follicular cells for example, constitutively produce very high levels of reactive oxygen species (J.E. Dumont, pers. commun.) although how this might relate to breast luminal cells remains unclear.

Conclusions and implications

Although there is nothing novel about the concept that the phenotype of a tumour should be influenced by the phenotype of its cell of origin, what is less widely appreciated is the possibility that the genotype of a tumour may at least in part be similarly predetermined. Perhaps the major implication of this idea is the realization that the correlation between a given gene mutation and a particular clinico-pathological behaviour (e.g. mp53 with poor prognosis in a subset of invasive breast cancers) may be an indirect one (both being determined by the underlying cell context). In such cases it follows that the search for a direct link between mutation and tumour behaviour will be potentially fruitless (although in the case of p53, secondary effects of mutation might be expected through loss of genomic stability). It is not surprising, therefore, that suggestions for how mp53 might cause increased breast cancer aggressiveness have been unconvincing (13)!

This reasoning can be extended to examples of tumour progression where an increase in tumour aggressiveness correlates with acquisition of p53 mutation. Again the realization that both may be the result of an underlying switch in phenotype re-orientates research efforts away from the search for additional somatic mutations and towards a greater understanding of the underlying epigenetic mechanism.

This concept also changes the evaluation of prognostic markers. p53 mutation may be a valuable negative prognostic marker in breast cancer for example, simply because it identifies those tumours that have a ‘stem cell’ origin. Viewed in this way, more weight should perhaps be given to evaluating other phenotypic markers related to the cell of origin (for example the pattern of intermediate filament expression), which may prove as useful as p53 mutation, but much easier to evaluate.

Finally, from the therapeutic standpoint, the existence of major cell-type differences in sensitivity to wt p53 raises several important issues in relation to novel therapies. There has been much excitement (68) surrounding the therapeutic potential of a mutant adenovirus that lacks the ability to inactivate host cell p53 and should therefore selectively replicate in and kill cancer cells lacking wt p53. The observations on breast and thyroid cells discussed above point, however, to the possibility that some normal cell types may be functionally p53 deficient, and hence would be potentially liable to the toxic action of such an agent. On a more positive note, if this same mechanism is the basis for tolerance of wt p53 in cancers derived from such cell types, it may represent an ideal target for therapy designed to antagonize the MDM2–p53 interaction (69). Either way it is clear that the influence of cell context is a major factor to be taken into account in the design and application of such new anticancer strategies.

References

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