EDITORIAL

At last, a predictive and prognostic marker for radiotherapy?

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See related research by Hu *et al.*, http://breast-cancer-research.com/content/12/2/R18

Abstract

Holliday junction recognition protein (HJURP) levels in breast cancer associate with both poor prognosis and an increased sensitivity to irradiation. Whilst, in part, this could be explained in relation to proliferation, it would not entirely account for the association with sensitivity to radiation. Thus, HJURP may have clinical potential as a marker of prognosis and radiation sensitivity; further validation with tissues from randomised controlled trials is needed. HJURP may represent the first in a class of proteins with roles in chromosome segregation and DNA repair that act as predictive biomarkers.

Introduction

Hu and colleagues [1] have risen to the challenge of seeking to identify a prognostic and predictive marker of sensitivity to radiotherapy in breast cancer. Radiotherapy for patients with breast cancer improves local disease control, and relapse free and overall survival [2]. Like most therapies, this comes at the cost of some morbidity [2,3], which is the driver for technical refinements in radiotherapy, including hypofractionation, partial breast radiation and intraoperative radiotherapy, with increasing use and development of radiotherapy predicted for the future [4]. There are significant benefits in targeting systemic breast cancer treatment, using, for example, oestrogen receptor (ER), or HER2 receptor expression. Transcriptome profiling may be used not only to categorise breast cancers, but in practice and randomised controlled trials to guide therapy [5]. In contrast, few inroads have been made into identifying prognostic or predictive biomarkers for radiotherapy in breast (or indeed any other) cancer [6].

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Hu and colleagues [1] have made a bold attempt to address both biomarker questions in a single study. In 130 patient samples and 4 breast cell lines, they examined Holliday junction recognition protein (HJURP), required for centromere protein A (CENPA) localisation [7-9] and involved in repairing double-strand DNA breaks [10]. By protein (western blot) and mRNA level (which at least in cell lines correlated), HJURP expression was higher in cancers than normal tissues and was associated with poor prognostic features, including ER-negative, high grade and high Ki67 proliferation index cancers. Remarkably, HJURP, divided empirically into high, mid and low tertiles, was an independent prognostic variable for disease free and overall survival in 130 women with breast cancer and outperformed many conventional prognostic features. The prognostic hypothesis was tested and replicated on transcriptome data from five further publicly available data sets, confirming the association between high HJURP mRNA and prognosis. However, an independent association with radiotherapy outcomes as opposed to overall systemic outcomes (disease-free survival and overall survival) requires elucidation. Furthermore, questions regarding differing radiotherapy regimens, breast conservation or mastectomy, extent of radiotherapy and differences in systemic therapy may all have a bearing on outcomes but were clearly beyond the remit of this study [1].

The allied mechanistic questions examined *in vitro* showed two breast cancer cell lines with high HJURP were more sensitive to radiation (via apoptosis) than two immortal lines with low levels of HJURP; HJURP levels were associated with CENPA, and HJURP knockdown reduced sensitivity to radiation. Subgroup analyses noted patients with high tumour HJURP given radiotherapy had a better disease-free survival than those who did not receive radiotherapy, suggesting the cell line studies were clinically relevant. Is HJURP the driving force for radiation sensitivity, or does it reflect another aspect of tumour pathobiology? If radiation sensitivity is related to the role of HJURP in DNA damage repair, cells with higher HJURP should show enhanced repair and, therefore, radiation resistance, contrary to the data

obtained. On the other hand, both HJURP and CENPA are cell cycle regulated to achieve their functions in chromosome segregation [8,9] and proliferating cells are generally radiosensitive compared to non-proliferating cells. HJURP may simply reflect proliferation, evidenced by the reduced proliferation in the HJURP knockdown cells, which become radioresistant. However, that HJURP is associated with radiation response suggests levels of HJURP are ineffective for repair, and the cells lack other repair pathways. Increased HJURP may therefore result from failed attempts to repair ongoing damage. Alternatively, increased HJURP may indicate a block in cell cycle at a stage that is susceptible to radiotherapy, leading to hyper-activation of HJURP (and CENPA). Indeed, proliferation itself (measured by Ki67) is not a strong pre-treatment indicator of response, whereas mitosis shows a significant association with chemo/radiotherapy outcome [11]. Thus, HJURP may act as a predictive marker because of its dual roles in accurate chromosome segregation during mitosis and in DNA repair and may represent the first example of this class of predictive biomarkers.

Regardless of the mechanism(s) involved, the prognostic potential will require testing in large randomised clinical trials of radiotherapy [3,12]. However, in most clinical and trials settings, formalin fixed paraffin embedded tissues may be the sole tissue resource available and while mRNA analyses are possible on such material, immunohistochemistry delineating the cell distribution of HJURP protein (cancer cell or stroma, tumour periphery, heterogeneous or homogeneous distribution) may be helpful. In trials, patient variables are balanced and should provide the potential to address the issue of sensitivity to radiation. A role for HJURP in normal (breast) tissues may also predict which patients might show increased sensitivity to radiotherapy and so indicate patients who would get excessive early or late radiotherapy effects [13].

While the data presented here [1] are inevitably preliminary, the ability to predict tumour sensitivity to radiotherapy in a way analogous to ER or HER2 is an intriguing prospect.

Conclusion

In HJURP, do we at last have a predictive and prognostic marker for who should (or should not) have radiotherapy? It is too soon to be sure, but HJURP clearly merits evaluation and requires validation as a prognostic and predictive marker in the multimodality treatment of breast cancer.

Abbreviations

CENPA = centromere protein A; ER = oestrogen receptor; HJURP = holliday junction recognition protein.

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