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IS CLINICAL RADIOSENSITIVITY A COMPLEX GENETICALLY CONTROLLED EVENT?

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New insights into molecular mechanisms responsible for cellular radiation response are coming from recent basic radiobiological studies. Preliminary data supporting the concept of clinical radiosensitivity as a complex genetically controlled event are available, and it seems reasonable to hypothesize that genes encoding for proteins implicated in known radiation-induced pathways, such as DNA repair, could influence normal tissue and tumor response to radiotherapy. Such genes could be considered as candidates for experimental studies and as targets for innovative therapies. Variants that could influence individual radiosensitivity have been recently identified, and specific Single Nucleotide Polymorphisms have been associated to the development of different radiation effects on normal tissues. Allelic architecture of complex traits able to modify phenotypes is difficult to be established, and different grades of interaction between common or rare genetic determinants may be present and should be considered. Many different experimental strategies could be investigated in the future, such as analysis of multiple genes in large irradiated patient cohorts strictly observed for radiation effects or identification of new candidate genes, with the aim of identifying factors that could be employed in predictive testing and individualization of radiation therapy on a genetic basis.

Key words: DNA repair, polymorphism, radiosensitivity.

Introduction

In recent years, much effort has been made to improve the basic knowledge of radiation effects on normal and neoplastic cells, looking for an integration of classical radiation biology with new emerging concepts from the fields of genetics and molecular biology. The advance has been substantial, with definition and clear description of several signaling pathways involved in cellular radiation response, but genetic determinants and molecular mechanisms of clinical therapeutic radiosensitivity are still poorly understood. Interindividual differences in the occurrence and severity of radiation effects are a very common event in radiation oncology. Furthermore, in the same patient a different grade of toxicity in different tissues may be observed. Despite the fact that multiple factors (age, nutritional status, coexisting morbidities, fractionation schedule, treatment volume, etc.) are responsible for this phenomenon, probably a more profound biological difference exists and contributes to interindividual variability of tumors and normal tissue radiation-induced reactions. Available data supporting the hypothesis that radiosensitivity is in fact influenced by genetic factors and preliminary results of genetic assays currently under investigation are presented and discussed, with the aim of delineating the potential future implications in the field of radiation oncology.

Genetic syndromes and *in vitro* assays

Strong evidence in favor of a genetic basis of radiation response originates from studies on patients with rare genetic syndromes such as ataxia telangiectasia, Fanconi's anemia, Nijmegen Breakage syndrome and Bloom's syndrome. A small number of case reports of patients affected by these diseases showed patterns of enhanced cellular and clinical radiosensitivity and increased susceptibility to cancer development[1,2]. These syndromes are clearly related to germ line mutations regarding genes involved in detection of DNA damage or DNA repair[3]. Mutations in repair genes have also been detected in patients with reported extreme radiosensitivity, even if not affected by any of these syndromes[2,4,5]. All of the cited genetic syndromes are very rare, characterized by Mendelian inheritance and probably of limited importance when addressing the issue of clinical radiosensitivity in a population of unselected cancer patients. However, as pointed out by different Authors[6,7], they could be considered as a "proof of principle" that clinical radiosensitivity is in fact determined by genetic factors.

The possible association between *in vitro* cell radiosensitivity and clinical patterns of sensitivity among unselected cancer patients is an experimental approach that can be considered: few data are available, but the correlation seems to be supported by a genetic basis.

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Some studies on "overeactors" have indicated that on the average these patients exhibit a higher *in vitro* radiosensitivity[8,9]. It has also been demonstrated that first-degree relatives of breast cancer patients with increased clinical radiosensitivity show increased *in vitro* radiosensitivity compared to controls[10,11].

Studies investigating the correlation between *in vitro* radiosensitivity (with a variety of biological end points) and clinical radiosensitivity in breast cancer patients have lead to contradictory results or have not been found to predict radiation toxic effects on normal tissues[12-15]. Twardella and Chang-Claude[13] reviewed 25 studies published between 1990 and 2000, with the aim of identifying which tests should be considered most promising. *In vitro* assays were classified in 4 groups: testing the ability to survive after exposure to radiation, cytogenetic tests evaluating the frequency of specific chromosomal aberrations in irradiated cells, a cell's ability to repair radiation-induced damages, other radiation-induced end points like apoptosis[13]. Most of these studies employed a study design that included patients previously submitted to radiation therapy and for whom the severity of side effects was already known. The biological end point of all the assays was an estimation of cellular effects in terms of "cell lethality" and a correlation with radiation-induced toxicity. An observation could be made about the fact that acute and late effects on normal tissues are now better understood and clearly different in their pathogenesis. For acute effects, the role of cellular response evaluated by *in vitro* tests appears more clear (even with contrasting experimental findings), whereas late effects are probably not entirely dependent on cell lethality and modulated by multiple factors (extracellular matrix response, inflammatory cytokines, vascular damage), making it more difficult to define a correlation with cellular response of irradiated cells.

Problems may also arise when evaluating late effects in terms of the choice of the "control" group, taking into account bias as prolonged survival (this is especially important in evaluating data of patients treated with aggressive regimens for tumors with a poor prognosis). Due to these considerations, Ferret and Hall[6] observed that the possibility to identify an *in vitro* assay showing sufficient sensitivity and specificity in detecting individuals who will probably develop acute or late clinical radiation toxicity is highly debatable[6]. Anyway, getting closer to the point of a genetic basis of clinical radiosensitivity, a consideration could be made about the fact that the weak correlation sometimes demonstrated between *in vitro* data and clinical data seems likely to depend on genetic factors. This hypothesis is supported by the current knowledge on biological events (DNA repair or apoptosis) that can be now clearly regarded as genetically controlled complex cellular phenomena.

Irradiated patient's genotypes and clinical radiosensitivity

Since the ATM (Ataxia Telangiectasia Mutated) protein plays a central role in the detection of DNA damage and in activating DNA repair pathways, many studies have addressed the hypothesis that heterozygosis for ATM mutation could be investigated in patients showing higher clinical radiosensitivity. *In vitro* cells with ATM heterozygosis show an intermediate radiosensitivity compared with cells from ataxia telangiectasia patients and healthy controls[3]. The frequency of heterozygosis in general population is estimated to be approximately 0.5-1%, with probably a higher frequency (3-5%) in a breast cancer patients' population, since ATM mutation carriers are at a 4-fold increased risk of breast cancer[16]. Many of these studies, retrospectively reviewing patients with severe reactions and looking for an unexpected frequency of mutations, did not demonstrate any correlation between ATM status and clinically enhanced radiosensitivity[17-22]. In a cohort of 13 patients known to be heterozygotes, no adverse reactions were recorded[17]. Iannuzzi *et al.*[23] reported 2 missense or synonymous ATM mutations in 3/3 breast cancer patients showing grade 3-4 subcutaneous late reactions after radiotherapy, whereas only 3 of 43 patients who did not develop this form of severe toxicity were carriers of ATM mutations. Interestingly, the authors did not employ the classical protein truncation test but a technique capable of detecting single base substitutions (denaturing high-performance liquid chromatography). Such alterations, especially if both alleles are affected, could be of greater importance for clinical radiosensitivity in terms of late reactions. No statistically significant correlation was found with early effects, and the finding is not clear if we think that ATM is the key sensor of DNA damage by ionizing radiation (especially double-strand breaks) and primarily involved in activating DNA repair pathways in all tissues.

Polymorphisms of the ATM gene were also investigated in a cohort of 254 breast cancer patients, 70 of them showing enhanced radiosensitivity[24]. A positive association was found between some variant alleles, with a complex finding regarding allelic architecture (homozygote/heterozygote state) and a difficult explanation from a mechanistic point of view, as pointed out by Authors.

Alterations in the breast cancer susceptibility gene BRCA1 also appear to be associated with radiosensitivity, based on results obtained from cell culture experiments using BRCA1 protein-deficient cells[25]. BRCA proteins are phosphorylated by ATM in response to DNA damage and form complexes with RAD51. On this basis, these proteins are believed to participate in DNA damage sensing and repair pathways. In addition, BRCA1 knocked-out mice are radiosensitives[26]. Carriers of BRCA1 or BRCA2 mutations may have enhanced clinical radiosensitivity. The frequency of these mutations in the general population is unknown[27]. In the only reported clinical investigation correlating BRCA status and enhanced clinical radiosensitivity, no mutations were found in 22 patients with severe normal tissue reactions (mutation detected with the protein truncation test)[28].

Gene mutations in DNA ligase IV[4], a protein involved in DNA repair, and Fanconi's anemia[29] gene have been reported in radiosensitive cancer patients, as anecdotal reports from a very small group of individuals investigated for these mutations.

Polymorphisms in XRCC1 and XRCC3, genes of DNA repair pathway, were strongly associated with clinical radiosensitivity in a paper by Price *et al.*[30] in 1997. However, it was a small study, including 34 healthy controls and 19 cancer patients, 8 classified as radiosensitives. XRCC1 knocked-out mice are extremely radiosensitive and XRCC1 is associated with genomic instability, including increased frequency of spontaneous or induced chromosome translocations or deletions[31]. The protein is implicated in every step of base excision repair. Moullan *et al.*[32] found a positive correlation between XRCC1 polymorphisms and adverse response to radiation therapy in a series of 70 radiosensitive breast cancer patients. The impact of these polymorphisms on phenotypes is unclear, particularly when multiple variants are present in a combined genotype. Wang *et al.*[33] correlated XRCC1 genotypes and level of *in vitro* chromosomal damage (obtained with radiomimetic drugs), finding a relation in individuals with a specific polymorphism. Andreassen *et al.*[34] established a significant correlation between 5 single nucleotide polymorphisms (SNPs) in 4 candidate genes, including XRCC1 and XRCC3, and risk of radiation-induced normal tissue late reactions in breast cancer patients. Interestingly, from these preliminary data it appears that the presence of multiple significant polymorphic variants of different genes in individual genotypes probably is able to influence clinical radiosensitivity in a complex way.

Quarnby *et al.*[35] found that certain SNPs in the TGFβ1 gene were associated with radiation-induced fibrosis. This multifunctional cytokine is involved in promoting tissue fibrosis, and pre-treatment plasma TGFβ1 levels are linked to the risk of developing subcutaneous fibrosis[36]. Homozygotes for these variants are 7-15 times more likely to develop severe fibrosis[35]. Polymorphisms of TGFβ1 were associated with increased risk of subcutaneous fibrosis in breast cancer patients also in Andreassen's paper[34].

Variants in the hHR21 gene have also been detected in radiosensitive cancer patients[36]. Six of 19 radiosensitive patients showed a variant in DNA sequence, not modifying the encoded amino acid. No information is available about the frequency in the general population.

The superoxide dismutase protein encoded by gene SOD2 is one of the major players in the defense against oxidative damage by radiation-induced free radicals. Polymorphisms in this candidate gene have been investigated and are believed to impact on protein function. Data from the study by Green *et al.*[37] showed a negative correlation between the investigated variant (Ala9Val) and radiotherapy reactions. The SOD2 codon 16 Val/Ala genotype was associated with the risk of subcutaneous fibrosis compared to the Val/Val genotype[34].

Genetic manipulation of radiosensitivity

Begg and Vens[38] recently reviewed a number of studies on genetic manipulation of radiosensitivity, considering different strategies. Two main approaches were described: to introduce or express antisense oligonucleotides which hybridize with mRNA and prevent translation; to overexpress a protein or a peptide (lacking an essential activity, called dominant negative) that competes with wildtype protein.

Poly ADO-ribose polymerase recognizes and binds to DNA strand breaks, activating the polymerase which then modifies chromatin structure[39,40]. Rudat *et al.*[41] demonstrated that expression of only the DNA binding domain leads to radiosensitization.

The G1/S checkpoint after ionizing radiation is p53 dependent, and abrogation of p53 function by overexpressing mutant p53 leads to increased resistance to radiation[42].

Signals from stimulatory or inhibitory pathways ultimately lead to transcription of genes. The cAMP response element (CRE) binding protein, CREB, is involved in initiating transcription from genes containing the CRE sequence in their promoters. Expression of dominant negative CREB proteins with lack of DNA binding activity can lead to radiosensitization[43]. Modification of other transcription factors can lead to changes in cell radiosensitivity: clones containing inducible dominant negative constructs to C-JUN and EGFR1 had reduced survival to irradiation[44].

Expression of ATM can be reduced using antisense constructs with concomitant increases in radiosensitivity[45,46].

Mammalian cells with homozygously deleted RAD54 (RAD52 genes family, involved in homologous recombination) showed markedly increased radiosensitivity[47], and antisense oligonucleotides to RAD51 have been shown to radiosensitize mouse glioma cells[48].

These studies provide a large number of possible targets potentially relevant to therapy, but are also another indirect evidence of the genetic basis of cellular radiation response.

Discussion

In a complete review on genetic basis of interindividual differences in normal tissues radiosensitivity, Andreassen *et al.*[7] defined and discussed the hypothesis that clinical radiosensitivity could be considered a genetic complex trait. This concept is based on the presented data on the genetic basis of radiation response, showing some evidence but also some unclear findings. The risk of so-called complex diseases depends on interactions between environmental factors and susceptibility alleles in a large number of genes[49]. It seems reasonable to suppose that clinical response to a course of radiotherapy should be regarded as a complex phenotype depending on the combined effects of several genetic alterations[7]. In this scenario, SNPs, previously regarded as genetic variations without functional signifi-

cance, now represent a very interesting field of research in radiation biology, showing early promising results as mentioned below. SNPs are potentially able to affect phenotype and could be located in regulatory regions, influencing gene expression, or in coding regions, causing amino acid changes that may alter protein function. SNPs in non-coding regions may affect DNA splicing or stability.

The allelic architecture of complex traits is clearly difficult to define in details, and different competing models could be considered. Probably, the basis is made up of common and rare genetic variants, and evidence is consistent with a model of genetic influence in which a large number of variants impact on radiosensitivity at different levels, generally or exclusively in certain types of tissues or through certain types of reactions[7]. Moreover, if clinical radiosensitivity is a phenomenon mainly dependent on a number of rare genetic variants in a large pool of potential loci, a high degree of heterogeneity is expected, with the same phenotype that could be determined by different genotypes. The candidate gene approach is based on the concept that genes known to be involved in radiation-induced phenotypes, like DNA repair genes (such as XRCC1, ATM) or pro-inflammatory cytokines genes (TGFβ1), should be the first to be investigated when designing experimental studies on the correlation between genetic variants and clinical radiosensitivity. This is a good way to study possible correlations with clinical radiosensitivity, but probably unable to explain some complex radiation-induced biological events that we still not know in details. The recent introduction of DNA microarray technology, with original data coming from early papers showing a correlation between specific gene expression profiles and radiosensitivity or the induction of expression of previously unexpected genes after *in vitro* irradiation[50-52] may help us to identify new candidate genes and to explain, from a genetic point of view, extremely different radiation effects in cancer patients. Preliminary findings on the correlation between radiation-induced toxicity and abnormal transcription responses to DNA damage are encouraging. A study by Rieger *et al.*[53] showed that transcriptional responses in 24 genes were able to predict radiation toxicity in 64% of 14 radiosensitive patients included in the study. Twenty of the 24 genes contributed to ionizing radiation response (DNA repair processes, stress response, ubiquitin/proteasome pathways, apoptosis, cell cycle control). A critical point in this approach, as pointed out by the Authors, is that it is not able to identify the genetic basis for toxicity, because predictive genes may not be mutated and may respond abnormally due to mutation in other genes, or as a result of a combined effect of polymorphisms in several genes. Complex interactions between genetic variants may be present and should be considered, such as the fact that environmental and epigenetic factors may influence radiosensitivity. Several ongoing trials are based on the genetic study of small groups of overreactors or large groups of consecutive patients carefully monitored for acute and late reactions (probably a more correct approach)[7]. The concept of clinical radiosensitivity as a genetically controlled complex event still remains to be fully understood, and many issues have to be dealt with, primarily the best experimental strategy. Anyway, analyzing available data, we could say that in the field of applied radiobiology the role of genetic studies is probably the key to better understand radiation effects on human tissues.

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