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Mutation Research 659 (2008) 49–55
Reviews in Mutation Research
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Review

# Overexpression of DNA repair genes is associated with metastasis: A new hypothesis

Alain Sarasin [a,*], Audrey Kauffmann [b]

[a] *Genomes and Cancers, FRE2939-CNRS, Institute Gustave Roussy, PR2, 39 rue Camille Desmoulins, 94805 Villejuif, France*
[b] *EMBL, European Bioinformatics Institute, Wellcome Trust Genome Campus, Hinxton, Cambridge CB10 1SD, United Kingdom*

Received 17 July 2007; received in revised form 17 December 2007; accepted 21 December 2007
Available online 16 January 2008

**Abstract**

Tumorigenesis is a multistep process, where it is believed that the transformation of normal cells into tumoral cells needs a succession of genetic and epigenetic changes, such as point mutations, chromosomal rearrangements, and changes in gene expression level. All these modifications are supposed to confer a selective advantage and to generate highly malignant cancer cells. Until recently, the same selection procedure of rare cells in the tumour mass was believed to be necessary for the metastatic process. Using gene expression profiling, several recent publications report that a gene expression signature could discriminate between primary tumours with high metastatic potentiality and poor clinical outcome, and primary tumours that are not going to metastasize. Analysis of the biological pathways associated with metastatic potential points to cell adhesion, angiogenesis, cell cycle regulation, initiation of DNA synthesis, and DNA repair. Analysing human primary malignant melanoma and various biological processes, we have shown that the overexpression of DNA repair pathways, particularly those involved in double-stand break repair and surveillance of the DNA replication forks, is associated with metastasis and poor patient survival [V. Winnepenninckx, V. Lazar, S. Michiels, P. Dessen, M. Stas, S.R. Alonso, M.F. Avril, P.L. Ortiz Romero, T. Robert, O. Balacescu, A.M. Eggermont, G. Lenoir, A. Sarasin, T. Tursz, J.J. van den Oord, A. Spatz, Gene expression profiling of primary cutaneous melanoma and clinical outcome, J. Natl. Cancer Inst. 98 (2006) 472–482]. These results, also found by analysing other types of human tumours, such as breast or bladder cancers, would clearly explain the high resistance of metastasis towards chemo- and radiotherapies. Our hypothesis is that genetic instability is absolutely necessary to go from normal cells to tumoral cells, but one needs some type of genetic stabilization, which can be obtained by overexpressing specific DNA repair genes, in order to produce primary tumour cells that are genetically stable enough to be able to invade and give rise to distant metastasis.


*Keywords:* DNA repair; Recombination; Metastasis; Melanoma; Xeroderma pigmentosum; Replication forks

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## 1. Introduction

For several decades, it was hypothesized that metastases were due to the selection of a small number of cells, within a large primary tumour, containing a specific set of genetic modifications that render them competent enough to leave the

* Corresponding author. Tel.: +33 1 42 11 63 28; fax: +33 1 42 11 50 08.
*E-mail address:* sarasin@igr.fr (A. Sarasin).

1383-5742/$ – see front matter 
doi:10.1016/j.mrrev.2007.12.002

original site, enter the blood stream, extravasate, overcome host defences and be able to grow as a vascularized metastatic colony in another organ. Several recent reports challenge the notion that rare metastatic cells pre-exist in the primary tumour by searching for a gene expression signature between metastatic and non-metastatic tumours [2]. Indeed, several gene expression signatures have been reported for primary tumours with metastatic capacity suggesting that most, if not all, of these primary tumour cells exhibit metastatic potency [1,3,4]. In several cases where this has been searched, the metastasis and primary tumour in the same patient show similar, if not identical, gene expression profiling [1,3,5]. This implies that the dominant cell population in the primary tumour is phenotypically and genotypically almost identical to the metastatic cells. The tumour cells should exhibit metastatic capacity and fitness rather than be selected by some kind of selection pressure during the metastatic process. This is confirmed by the fact that patients whose primary tumour bore a metastasis-associated gene expression profile, such as found with lung, breast and melanoma tumours, had a significant shorter survival as compared to patients whose tumours did not express this profile [1,3]. Numerous genes have been associated with a gene expression signature feature of metastasis (cell cycle regulation, DNA replication, DNA repair) and many biological processes have already been characterized as directly related to metastasis [6–8]. Among these genes, we have particularly focused on those involved in the maintenance of genetic stability in human cells in order to determine whether variations in the expression of repair genes have any association with metastatic risk. On purpose, this review does not take into account the other well-characterized biological processes already known as implicated in metastasis progression.

## 2. DNA repair pathways

It is very well known that abnormal regulation of or mutation in DNA repair genes can lead to diseases very often associated with predisposition to and high risk of cancer development. This is basically due to the fact that cells are constantly submitted to many DNA lesions due to exogenous environmental insults such as UV light, ionizing radiation, genotoxic chemicals, or to endogenous processes such as reactive oxygen species (ROS) produced in mitochondria during the production of energy and therefore the absence of a full DNA repair process will lead to the accumulation of DNA lesions, to an increasing rate of mutagenesis and finally to tumour initiation and progression.

Four major repair pathways are operating in all living cells: base excision repair (BER), nucleotide excision repair (NER), mismatch repair (MMR) and recombination repair.

Base excision repair is responsible for repairing damaged bases or single-strand breaks caused by spontaneous chemical modifications (such as deamination, depurination, hydrolysis) or to exogenous agents (particularly ROS, UVA or ionizing radiation) [9]. The reaction is initiated by specific DNA glycosylases that repair only a limited number of lesions. The 8-oxo-guanine is the most studied base induced by ROS. It is repaired by three different pathways involving the *hOGG1*, *hMYH* and *hMTH1* genes. Repair of this lesion is very important because it is a direct mutagen due to its pairing with A during DNA replication. Deficiency in BER has not been associated, up to now, with human diseases, except one case of recessive predisposition to colorectal cancer linked to germinal mutation on the *hMYH* gene [10].

Nucleotide excision repair is a multistep process able to repair bulky DNA damage produced by UV or chemicals, for instance. In human cells, about 30 different proteins are necessary to allow a full error-free repair. Individuals with inherited defects in NER can exhibit several types of diseases such as xeroderma pigmentosum (XP), trichothiodystrophy (TTD) or cockayne syndrome (CS). XP patients mutated in one of the seven XP genes (*XPA* to *XPG*) show hypersensitivity to UV and a very high susceptibility to develop skin cancers in exposed skin areas [11]. Because some of the DNA repair proteins are also involved in the regulation of RNA synthesis initiation, some patients mutated on the *XPB*, *XPD* or *XPG* genes show some transcription defects, which are obvious in TTD and CS syndromes [12]. These two syndromes are associated with neurological disorders and ageing but not with cancer predisposition [13].

In the absence of a full repair of bulky lesions before DNA synthesis occurs, replicative DNA polymerases are blocked by these lesions and eventually distributive and error-prone translesion polymerases (TLS) are able to take over and replicate past the lesions. This pathway could be more or less mutagenic depending upon the types of lesions to bypass and the types of TLS polymerases used. In the case of UV-induced DNA damage, the TLS polymerase eta is the least mutagenic one. XP variant patients, who exhibit inherited mutations on the *POLeta* gene, use another TLS polymerase, which is more error-prone. These patients show hypersensitivity to UV and predisposition to skin cancers due to this higher mutagenic activity [14,15].

Mismatch repair is a post-replicative repair process able to remove mispaired bases and insertion/deletion that arise between microsatellite sequences during DNA replication. The fidelity of normal DNA synthesis in human cells is around $10^{-6}$ before MMR and increases around $10^{-9}$ after MMR [16]. Defective MMR results in a higher spontaneous mutation frequency and microsatellite instability (MSI). This is usually caused by mutations in one of the MMR proteins involved in the recognition process such as the *MutS* and the *MutL* heterodimers. Germline mutations of these genes give rise to an inherited syndrome associated with predisposition to colorectal cancers (HNPCC for hereditary non-polyposis colorectal cancer), endometrium or gastric cancers. Germline or sporadic MMR-deficient tumours show microsatellite instability that can be recognized and help the clinicians give the best specific treatments for these tumours. MSI colorectal tumours are more sensitive than the others to some topoisomerase inhibitors such as camptothecin or etoposide [17]. The prognosis is usually better than for the non-MSI tumours [18]. MMR-deficient diseases are probably the most frequent syndromes with cancer predisposition among DNA repair-deficient diseases.

Double-strand breaks (DSB) are caused spontaneously during normal DNA synthesis and immunoglobulin diversification as well as following DNA insults due to ionizing radiation, ROS and antitumoral drugs. DSB as well as crosslinks (CLs) represent the most severe DNA damage because the genetic information is lost on the two strands of the helix at the same site. Efficient repair of these lesions is done by two specific recombination pathways: the homologous one (HR) and the non-homologous end joining (NHEJ) process. The DSB is recognized by the MRN complex (Mre11, Rad50 and Nbs1 proteins) that allows the DNA end resection to yield 3′-ssDNA tails that will start strand exchange with the homologous duplex DNA catalyzed by the RAD51, RAD52 and RAD 54 complexes. While the HR is supposed to be error-free because the repair enzymes use the homologous sequences to repair the breaks, the NHEJ gives rise to mutations and particularly to deletions due to religation between the two ends in each side of the damage. This pathway is often associated with deletions, loss of heterozygosity and chromosomal translocations, which is involved in the multistep process of tumorigenesis [19,20].

## 3. Are the primary tumours from DNA repair-deficient patients less aggressive than those from the general population?

Several studies report that cancer cells exhibit a mutator phenotype leading to numerous chromosomal modifications, microsatellite instability and elevated frequencies of point mutations [21]. These genomic aberrations explain how a normal diploid cell, at a given position in the body, could be sequentially modified in order to produce a primary tumour at the same site. Because of the numerous steps in which the integrity of the tumoral cell metabolism is probably impaired, can such highly modified genomes allow the metastatic process to occur?

This is reminiscent of the competition between MMR-deficient bacteria that exhibit a very high level of spontaneous mutations and wildtype bacteria in the same organism. MMR-deficient bacteria show an initial advantage imputable to a faster adaptation to the environment. However, if the environment is modified, such as transmission to another organism or recolonization, then the competitiveness of the mutated bacteria is lost and deleterious mutations often appear [22,23]. If this result can be translated to human tumours, this would indicate that highly mutagenized primary tumour cells have difficulties to move and colonize distant organs in other environment. Stabilization of the mutator phenotype in a large sense or increased DNA repair could be a way to allow a better success during the metastatic process.

Apart from HNPPC, which are due to germline mutations in MMR genes, microsatellite instability is also observed in 15% sporadic colorectal cancer (CRC). The defect in MMR not only induces a general mutator effect, but due to mononucleotide repeats in coding sequences, induces also numerous gene inactivations. In most CRC, it has been shown that these gene inactivations concern DNA damage signalling, DSB repair and MMR [24]. This result nicely explains the specific hypersensitivity of MSI CRC to bleomycin, a DSB inducer, and camptothecin, a topoisomerase I inhibitor [25]. These tumours are particularly deficient in the repair pathways we have shown to be overexpressed in primary melanoma that are going to metastasize [1]. Several genes are in common between both systems, such as *MSH6*, *BLM*, *XRCC2*, *RAD50* genes. Of course, not all the genes can be found because they need to contain mononucleotide repeats. Interestingly enough, NER or BER genes containing repeat sequences are not found particularly mutated in MSI CRC, as we did not find them involved in the metastasis risk. Indeed, MSI is associated with a significant survival advantage independently of all standard prognostic factors (hazard ratio: 0.42) [18] (Table 1). Regardless of the depth of the tumours, MSI CRC show a decrease likelihood of metastasis to regional or distant organs (odds ratio: 0.33 and 0.49, respectively) [18]. Lymphocyte infiltration is commonly seen in MSI CRC, suggesting the presence of immunogenic proteins that may be produced by the high mutator phenotype of these cells [26].

Table 1
Relationships between genetic instability and risk of metastasis

| Tumour types (Ref.) | Genomic instability of the primary tumour[a] | Risk of metastasis | Association with overall survival or DMFS[b] | Sensitivity to chemotherapeutic regimen |
|---|---|---|---|---|
| Primary malignant melanoma [1] | Probably yes | Low | Yes | Low |
| | Probably no | High | No | Very low |
| MMR—deficient colorectal cancers [24,25] | Yes | Low | Yes | High |
| Xeroderma pigmentosum: malignant melanoma [29] | Yes | Low | Yes | ? |
| Bladder tumours [32] | Probably yes | Low | Yes | ? |
| | Probably no | High | No | ? |
| Breast cancers [3] | Probably yes | Low | Yes | ? |
| | Probably no | High | No | ? |
| Breast cancers [33] | Probably yes | Low | Yes | ? |
| | Probably no | High | No | ? |

[a] "Probably no" indicates that, because one sees an increase in the expression of some DNA repair genes, one can hypothesize that the tumour cells will be genetically more stable.
[b] DMFS indicates distant metastasis free survival.

Xeroderma pigmentosum is a rare inherited, autosomal and recessive disease caused by defect in NER. This deficiency is accompanied by extreme sun-sensitivity and a very high frequency of early skin cancers including malignant melanoma [11]. The absence of repair of UV-induced DNA lesions gives rise to high mutation rates in skin cells and skin tumours and numerous mutated genes have been found in these tumours including the *p53* gene and several oncogenes [27,28]. We can, therefore, consider the XP tumours as expressing a high mutator phenotype following sun exposure. Interestingly enough, the XP melanomas are considered to be of better prognosis than in the general population [29]. Although these tumours are able to metastasize, they are not as aggressive and of vital prognosis as for the DNA repair-proficient patients (Table 1).

## 4. Are the DNA repair pathways involved in the metastasis risk?

From the previous chapter, it is clear that DNA repair is absolutely vital for a normal life because inherited diseases caused by defects in DNA repair activity are associated with shorter life expectancy, predisposition to cancer and/or ageing. Indeed, all DNA repair pathways are much conserved from bacteria to man. Although it is evident that DNA repair defects increase the speed of primary tumour development, the main subject of this review and the question we ask here is to determine whether DNA repair efficacy is involved in the risk of metastasis of a given primary tumour. In order to answer this question, we analysed the results published in the literature concerning the gene expression signature, obtained using DNA microarrays, between metastatic and non-metastatic primary tumours. This study was done using a new bioinformatics tool, SBIME (Searching for a Biological Interpretation of Microarray Experiments), allowing us to analyse the whole metabolic pathways associated with the metastatic risk. SBIME performs an ANOVA calculated on the logarithm gene expression (log (ratio)) [30]. This ANOVA compares tumours that will metastasize with tumours that will not metastasize and we consider genes with a $p$-value lower than $1.0 \times 10^{-2}$ as being differentially expressed between the two groups. For each pathway, SBIME then estimates the significance of the proportion of differentially expressed genes as compared to the total proportion of significant genes on the array, by a Fisher's exact test. The pathway we focused on is the DNA repair as described in the Gene Ontology database [31] that we manually curated because of missing well-known repair genes and on the contrary some genes indexed did not really belong to repair process. The lists of DNA repair genes are attached to our previous paper [30].

We applied this method on five published microarray data sets for which the row data necessary to feed the SBIME programme were available: our melanoma study [1], one study of bladder carcinoma [32], two different studies of breast cancer [3,33] and a study on squamous carcinoma of the oral cavity [34]. The whole DNA repair pathway presents a significant proportion of differentially expressed genes between metastatic and non-metastatic primary tumours in four out of these five studies [1,3,32,33]. In the four cases, the majority of the significant repair genes are overexpressed in the primary tumours that are going to metastasize. The proportion of significant repair genes that are overexpressed in cancers that will metastasize reaches 90% in melanomas, 82% in bladder carcinomas, 80% in the van't Veer studied breast cancers and 58% in the breast cancers from Wang's study with $p$ values varying from $1.4 \times 10^{-2}$ to $1.4 \times 10^{-16}$ (Fig. 1).

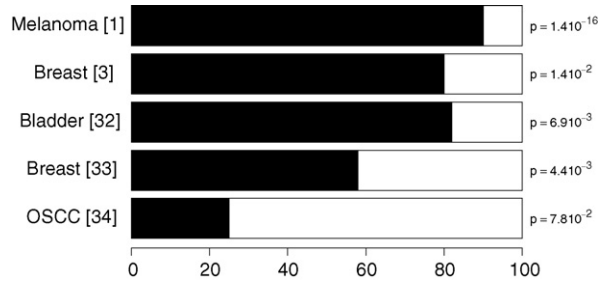


Fig. 1. Proportion of overexpressed and underexpressed significant repair genes among the literature studies. Bars represent the proportion of significant genes (ANOVA, $p < 0.01$) involved in DNA repair pathways (black: M+ > M−; white: M− > M+, with M+ meaning that the primary tumours will metastasize and M− meaning that the primary tumours will not metastasize). $p$-Value indicated on the right of the bars are obtained with the Fisher's exact test performed by SBIME. A $p$-value less than 0.01 denotes a statistically significant overrepresentation of the repair genes in one of the two classes (M+ or M−).

In the case of the squamous carcinoma of the oral cavity, the repair genes do not seem significantly deregulated between the two groups of tumours. None of the major genes found with the other types of tumours, such as those involved in loading clamps, BRCA/FANC and the homologous recombination pathways are overexpressed in the squamous carcinoma of the oral cavity (Supplementary Table 1). The squamous cell carcinomas originated in the oral cavity (OSCC) have typically a presentation with 50% of patients with lymph node metastasis [34]. Contrary to the previous four cancer localizations, metastases at distant sites are very rare in OSCC. The difference in DNA repair gene expression between distant metastasis and lymph node involvement may be explained by complete physiological and biological differences between these two types of primary tumour invasion. It would be interesting to confirm this hypothesis on other types of primary tumours mainly associated with only lymph node invasion.

These results clearly show that DNA repair pathways, in a large sense, are overexpressed in primary tumours associated with high risk of distant metastasis. This seems to be true for several different types of tumours (Table 1). Among a list of 234 DNA repair genes, 204 are present on the DNA microarrays used in the study of human primary melanoma and 48 of these genes are differentially expressed between the tumours that are going to metastasize versus the ones that are not going to do so [30]. In the case of human primary bladder tumours, 148 of the 234 DNA repair genes are found on the microarrays [32] with 11 of them that are differentially expressed between the tumours that will metastasize and the one that will not. To end, 198 and 203 DNA repair genes are, respectively, present on the microarrays from van't Veer et al. study [3] and Wang et al.

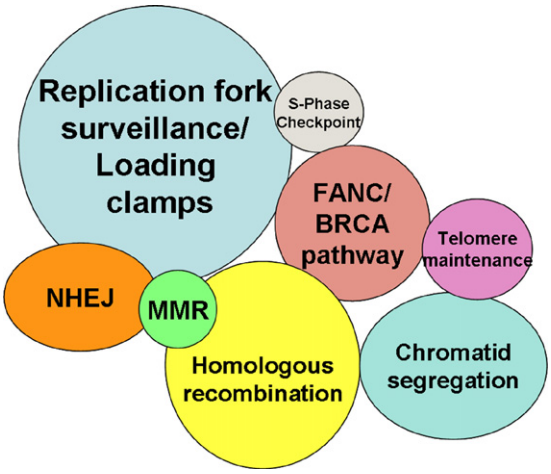


Fig. 2. Major DNA repair pathways which overexpression is associated with the metastasis risk. The size of each circle is roughly proportional to the number of genes involved found differentially expressed in the analysed studies.

study [33], with 15 and 19 that are differentially expressed between metastatic and no metastatic breast primary tumours. Among these repair pathways, those implicated in NER and BER are clearly not implicated in the metastatic risk. In contrast, the genes involved in surveillance and recovery of stalled DNA replication forks such as loading clamps, FANC/BRCA and homologous recombination pathways are the most represented among the overexpressed genes in primary tumours that will metastasize [1,30]. A few number of genes involved in S-phase checkpoints, chromatid segregation and telomere maintenance are also involved (Fig. 2). Interestingly, several MMR genes are also implicated, but one can imagine they are there because of their role at the replication origins to allow a faithful recovery of stalled forks rather than acting on the fidelity of replication. MMR proteins appear, indeed, to be present and necessary at recombination structures. A complete list of DNA repair genes found in these 4 tumour types is given in Supplementary Table 1.

It is obvious that overexpression of probes as determined by DNA microarrays is not a proof of an increased enzymatic activity. Although validation by immunhistochemistry has been done for a couple of genes [1], we have not tried to search for an increased activity of DNA repair proteins. This validation will be carried out in the future on fresh tumour samples to validate this hypothesis. However, one has to take into account the difficulty of such experiment using fresh tissues from different donors to quantify very sophisticated pathways such as homologous recombination.

The molecular mechanism underlying the overexpression of so many genes is still unknown. Two possible explanations can be proposed: these genes are somehow under a common general regulation process we do not know the origin of, or their overexpression has been independently selected during the tumorigenesis pathway. The latter is highly difficult to imagine because of the large number of genes involved, therefore the search for (a) common activator(s) is of prime interest to propose an easy way to predict metastatic risk and to search for specific drug targeting. Half of the DNA repair genes overexpressed in metastatic primary melanoma are involved in direct or indirect interactions with the p53 pathway [30].

## 5. Conclusions

Tumour cells that have the capacity to metastasize probably exhibit higher speed of replication and cell division. These processes need to be tightly controlled to avoid the production of unstable and abnormal cells that will be unable to produce distant metastasis. Increasing DNA repair gene expression should stabilize the genome of primary tumour cells to allow them enough stability for invasiveness. As indicated in Fig. 3, a primary tumour is caused by the accumulation of multiple genomic modifications. In some cases the expression signature present in the primary tumours corresponds to a specific phenotype associated with metastatic potency. Hence, stabilization of the genomic information is enough to allow distant metastasis with high efficacy. In some other cases, the gene expression spectrum is not in favour of metastasis production, and tumour cells may need another series of genomic modifications followed by selection to eventually lead to metastasis (Fig. 3).

The recent discovery [1–5] suggesting that the predominant genetic status of a primary tumour, rather than the selection of rare cells, will produce metastasis, is of prime interest. Besides the mechanistic understanding of the metastatic process, the possibility to predict the clinical prognosis of metastasis at the time of diagnosis of the primary tumour is obviously fundamental for the patient. Many patients who are not going to develop metastasis are, however, often treated by difficult, long and expensive antitumoral regimens, which are indeed unnecessary. In contrast, for patients for whom we are sure the tumour will rapidly metastasize, more emphasis

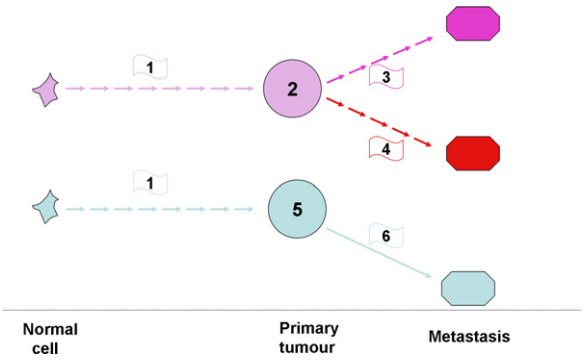


Fig. 3. Schematic representation of metastasis development according to gene expression signatures between primary tumours and metastasis. Row **1** indicates the numerous genomic modifications (mutations, LOH, translocations, chromosomal rearrangements) necessary to transform a normal diploid human cell into a primary tumour. If primary tumour **2** contains very rare metastatic clones, several selections need to occur (indicated by rows **3** and **4**) in order that these clones are able to grow and produce a metastasis in a distant organ. Several of these selections may occur by chance and therefore different gene expression signatures between metastasis and primary tumours are expected. If primary tumour **5** already contains essentially all cells with a metastatic potential, then no selection at all or very little changes (represented by row **6**) in gene expression levels are expected between primary tumour and metastasis. This has been found in several classes of tumours.

should be given to an early heavy treatment and stronger follow-up.

Moreover, these gene expression signatures of metastatic potential should help to envisage new treatment targets. Although we believe that DNA repair processes are essential to avoid the appearance of primary tumours, specific inhibition of DNA repair, particularly the recombination pathways, may lead to a treatment of metastasis development or at least to the diminution of the aggressiveness of these clones. Destroying the capacity of metastatic cells to perform error-free repair of their genome may lead to genetic instability and auto-destruction of the metastatic clones. It is also possible that the cellular production of mutated proteins allows a better host immunological response, leading to the destruction of unstable clones by the local host environment.

## Acknowledgements

The authors are thankful to Prof. Jean-Claude Ehrhart for the critical reading of this paper. This work has been granted to AS by the ''Cancéropole Ile-de-France'' and the ''Institut National du Cancer'', Paris, France).

## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.mrrev.2007.12.002.

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