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The Endothelin Axis in DNA Damage and Repair: The Cancer Paradigm

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1. Introduction

Maintenance of genomic stability is central to cellular homeostasis and self defense from environmental or intracellular inducers of DNA damage. Depending on the type of DNA lesion, several DNA repair mechanisms exist. Each major DNA repair process involves the detection of DNA damage, the accumulation of DNA repair factors at the site of damage and finally the physical repair of the lesion [1, 2].

The simplest, single enzyme DNA repair pathway is direct reversal or repair (DR) which is effected by O6-methylguanine-methyltransferase (MGMT), which is an enzyme that directly reverses DNA alkylation damage at the O6 position of guanine residues [2].

The mismatch repair (MMR) pathway is responsible for repair of 'insertion and deletion' loops that form during DNA replication [3]. These errors cause base 'mismatches' in the DNA sequence that distort the helical structure of DNA. Key MMR proteins MSH2 and MLH1 are involved in detection of this distortion and excision of the mismatch site which is then followed by new DNA synthesis.

DR is closely associated with MMR as a reduction in MGMT expression resulting from gene promoter methylation in some tumors, such as gliomas, results in recognition of resultant DNA mismatches by MMR and ultimate stimulation of pro-apoptotic signals after treatment with the alkylating agent temozolomide [4].

Repair of DNA alkylation products, oxidative lesions and single strand breaks (SSBs) is orchestrated by the base excision repair (BER) pathway. BER comprises a first step of removal of the damaged base from the double DNA helix which is followed by excision of the

“damaged” area and replacement with newly synthesized DNA [5]. The enzymes poly (ADP-ribose) polymerase 1 and 2 (PARP1 and PARP2) play a key role in this process, acting as sensors of DNA damage and signal transducers for subsequent repair. Bulky SSBs, including those caused by ultraviolet radiation are repaired by the nucleotide excision repair (NER) pathway [6]. NER is divided into two sub-pathways, transcription-coupled repair (TCR) and global-genome repair (GGR). TCR is involved in repair of lesions that block the elongating RNA polymerase during transcription, whereas GGR repairs lesions that disrupt base pairing and distort the DNA helix. The actual mechanism through which NER is effected involves surrounding of the lesion, excision by the protein Excision repair cross-complementing protein 1 (ERCC1) and replacement with the use of the normal DNA replication machinery [6].

As opposed to SSBs, repair of double strand breaks (DSBs) depends on homologous recombination (HR) and non-homologous end joining (NHEJ) repair pathways. Homologous recombination involves the resection of DNA sequence around the lesion using the homologous sister chromatid as a template for new DNA synthesis. Most important HR repair factors include BRCA1, BRCA2, RAD51 and PALB2 [7]. With regard to NHEJ, DNA repair involves direct ligation of the ends between DSBs in an error-prone manner. As such, deletion or mutation of DNA sequences at or around the DSB site may occur [8].

Translesion synthesis and template switching are another two DNA repair pathways which allow DNA to continue to replicate in the presence of DNA lesions that would otherwise halt the process. In translesion synthesis, low-fidelity ‘translesion’ DNA polymerases are recruited to the DNA damage site in order to enable DNA synthesis during DNA replication. When the replication fork passes the DNA damage site, the low-fidelity DNA polymerases are replaced with the usual high-fidelity enzyme to allow normal DNA synthesis. Template switching involves bypass of the DNA damage at the replication fork by leaving a gap in DNA synthesis opposite the lesion. When the replication fork passes the DNA damage site, the single-strand gap is repaired using template DNA on a sister chromatid, as in HR repair [2].

The concept of targeting DNA repair pathways is supported by an increasing amount of evidence as a potent contributor to the effectiveness of conventional chemotherapy or radiotherapy and even as a promising monotherapy in tumors with known DNA repair deficiencies. Thus, sensitization of cancer cells to DNA damaging agents with DNA repair inhibitors is an evolving field of cancer research [9]. Further to clinical development of newly synthesized agents, the exploitation of already existing targeted agents inhibiting growth signaling pathways would seem a reasonable strategy, given that in most cases of genotoxic stress, anti-apoptotic and prosurvival signals are activated, rendering the DNA repair machinery a vital cellular tool for survival and proliferation.

The endothelin (ET) axis is such a drugable target and comprises three 21-amino acid peptides, endothelin-1 (ET-1), ET-2 and ET-3, two G-protein coupled receptor (GPCR) subtypes, endothelin A (ETRA) and endothelin B (ETRB) and the endothelin-converting enzyme (ECE), which catalyzes the generation of active ET [10]. The ET axis has been previously implicated in the response of endothelial cells to ionizing radiation and it

could be used as a biomarker for irradiation of endothelial tissues, based on evidence of transient increase of ET-1 mRNA accumulation in human vein endothelial cells (HUVECs), followed by a net increase of ET-1 and big ET-1 peptides in the cytoplasm after irradiation [11]. In addition, ETRA downregulation was recently identified as part of the transcriptional response of endothelial lymphatic cells exhibiting a chronic oxidative stress signature in radiation-induced post-radiotherapy breast angiosarcomas [12]. In general, the ET axis is a key regulator of oncogenic processes, as it was shown to be expressed and active in various cancer and stromal cells leading to autocrine and paracrine feedback signaling loops promoting tumor growth and cell proliferation, escape from apoptosis, angiogenesis, invasion and metastatic dissemination, aberrant osteogenesis and modification of nociceptive stimuli [13]. ET-1 is the most prevalent and well-studied ET family member. ET-1 downstream signaling is mediated by ETRA and ETRB whereas ET-1 clearance uses two pathways: a) ETB-mediated uptake and subsequent lysosomal degradation [14] b) ET-1 cleavage by the extracellular membrane enzyme neutral endopeptidase 24.11 (NEP, neprilysin, CD10) [15].

Aberration of the ET axis, particularly in terms of ET-1 overexpression or/and perturbation of ETRA to ETRB expression ratio have been consistently associated with malignant transformation and progression in colorectal and prostate tissues. ET-1 plasma levels were found to be increased in patients with colorectal cancer as well as in a rat model of colorectal cancer in which inhibition of ETAR with a selective antagonist (BQ123) significantly reduced tumour weight of metastatic lesions to the liver. Further, ETBR gene promoter hypermethylation is a frequent event leading to reduced or absent receptor expression [16-18]. Increased ETAR expression was observed with advancing tumour stage and grade in patients with local and metastatic prostate cancer [19]. In addition, reduced ET-1 clearance due to attenuated levels of ETBR and NEP expression further promote increased local ET-1 levels [19, 20]. ET-1 and ETRA are greatly involved in ovarian carcinogenesis and progression and were both found to be overexpressed in primary and metastatic ovarian tumours [21-23].

With regard to ET-2, emerging data have demonstrated an association between upregulation of ET-2 transcript levels in human breast cancer cell lines [24] as well as in basal cell carcinoma as a result of increased Hedgehog signaling [25]. Investigation of the role of ET-3 in cancer has recently revealed a significant reduction in both ET-3 transcript and protein levels in breast cancer tissues compared with normal tissue, due to hypermethylation of the ET-3 promoter and subsequent gene silencing [26]. Thus, ET-3 might be considered a signaling factor with tumor suppressor properties, as opposed to ET-1 and ET-2 [27].

2. DNA damage and the Endothelin Axis

The best example of the involvement of the ET axis in the cellular response after exposure to DNA damage is the tanning response. After UV irradiation of keratinocytes, upregulation of a plethora of growth and survival factors occurs, including ET-1, bFGF, NGF, MSH, ACTH, P-LPH and P-endorphin. The essential roles of the tanning response are prevention of fur-

ther DNA damage or/and apoptosis of stressed cells and induction of melanogenesis [28-30]. A better understanding of the signaling events following UV-mediated stimulation of melanogenesis might enable selective manipulation of these signaling events with the aim of reducing or/and preventing the damaging effects of UV skin irradiation.

ET-1 has emerged as an excellent inducer of melanogenesis and melanocyte growth, promoting increased tyrosinase activity after binding to a high-affinity surface receptor [31]. ET-1 was also shown to enhance melanocyte dendricity and to act synergistically with other factors in UV-irradiated keratinocyte-conditioned medium, whereas this effect was abolished by addition of anti - ET-1 antibodies [30]. Thus, ET-1 is the major additional dendricity factor produced by UV- irradiated keratinocytes, although it is not a major factor in the absence of ultraviolet irradiation. Further, incubation of human melanocytes with the same medium resulted in substantial increase in melanin synthesis which was abrogated by anti - ET-1 antibodies [30]. Treatment of cultured melanocytes alone with ET-1 rapidly increased tyrosinase activity and melanogenesis and was responsible for transcriptional upregulation of tyrosinase and tyrosine-related protein -1 (TRP-1) [32]. Exposure of human epidermis to a moderate dose of UV radiation led to a significant upregulation of ET-1, interleukin (IL)-1 and tyrosinase gene transcripts. Given that UV irradiation induces IL-1 in keratinocytes, and IL-1 promotes ET-1 expression in an autocrine manner in the same cells, it is most likely that subsequent ET-1 release to neighboring melanocytes leads to increased tyrosinase mRNA, protein and activity, as well as to an increase in melanocyte population. This sequence of events, in which ET-1 seems to play a key role, has been suggested as a proposed model of the tanning response *in vivo* [32, 33].

A key transcriptional factor responsible for skin homeostasis after UV exposure is retinoid X receptor α (RXR α). Retinoids have been shown to regulate skin development, differentiation, and homeostasis, which are mediated by nuclear receptors such as retinoid acid receptors and retinoid X receptors (RXRs) [34, 35]. RXR α is the most abundant RXR isoform in skin and is implicated in the regulation of oxidative DNA damage and skin apoptosis and proliferation mechanisms of epidermal and dermal melanocytes following UV irradiation. This is mostly effected through regulation of secreted paracrine factors involved in the crosstalk between keratinocytes and melanocytes. Increased secretion of mitogenic paracrine factors, including ET-1, from mutated keratinocytes lacking RXR led to a significant increase in melanocytes after culture with conditioned keratinocyte medium following UV irradiation. Given that ET-1 was previously shown to regulate melanocyte proliferation and melanogenesis [36, 37] and that p53 upregulates ET-1 in UV irradiated keratinocytes [38, 39], it was suggested that p53 might be the link between RXR α and ET-1. However no recruitment of RXR α was found on the p53 promoter [40]. It is therefore possible that RXR α may directly or indirectly modulate expression of ET-1 and other paracrine survival factors to regulate melanocyte homeostasis [41].

ETRB was found to be expressed in human glioma cells [42, 43]. Based on this finding, treatment with ETRB inhibitors led to induction of cell cycle arrest and apoptosis. This was at least partially explained by DNA damage-mediated induction of genes encoding Growth Arrest and DNA Damage-inducible (GADD)153, GADD45A, GADD34, sestrin 2 and death receptor 5 (DR5). Up-regulation of the same genes was also observed in human melanoma

cell lines under the same conditions [44]. This evidence suggests that ETRB inhibition causes induction of DNA damage response mediators.

The central role of ET axis signaling in glioblastoma (GBM) was further evidenced by the emergence of ET-3 overexpression in GBM stem cells (GSC). Serum-induced proliferation and subsequent differentiation was associated with reduced ET-3 secretion and down-regulation of genes related with stemness, while upregulation of ET-1 and YKL-40 gene products. This was also evidenced in tissues from patients with GBM which were found to have low ET3 but high ET-1 and YKL-40 transcript levels. When the ET3/ETRB cascade was blocked either with the use of an ETRB antagonist or ET-3 RNA interference (siRNA), a plethora of genes were found to be downregulated, most of which were involved in cytoskeleton organization, pause of growth and differentiation, and DNA repair. With regard to the latter, most important DNA damage control and repair genes involved were found to be NIPBL (Nipped-B homolog), DHX9 [DEAH (Asp-Glu-Ala-His) box polypeptide 9], GTSE1 (G-2 and S-phase expressed 1), and RIF1 (RAP1 interacting factor homolog). These data support the existence of an intimate relation between ET-3/ETB signaling and maintenance of GSC phenotype in terms of migration, undifferentiation, and survival [45]. A simplified schema of the role of ET axis in DNA damage control and repair in GBM cells is depicted in Figure 1.

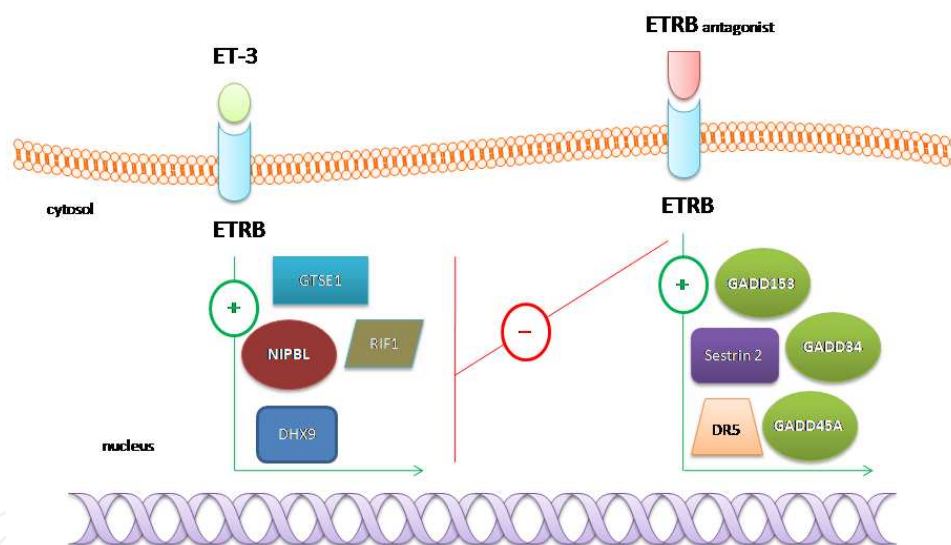


Figure 1. Simplified schema of the DNA damage control and repair transcriptional regulation by the ET axis in GBM cells.

An intriguing part of the association between ETRB and response to DNA damage in both glioma and melanoma cells is that cellular death was not found to be dependent on ETRB signaling. First, treatment with ETRB antagonists was able to reduce cell viability at higher doses compared to the ones required to inhibit the ET-1–ETRB ligation. Second, ETRB antagonism in glioma cells with undetectable ETRB was able to induce cell death. Third, experimental reduction of ETRB expression in other cell lines by >90% had no effect on cell viability of glioma or melanoma cells [44]. It might be hypothesized that melanoma and glioma cells follow a distinct pattern of response to treatment with ETRB antagonists that should be further elucidated.

3. DNA repair and the Endothelin axis

A significant amount of data supports a pro-survival effect of ET-1 after UV irradiation on human melanocytes. The anti-apoptotic role of ET-1 was shown to be a receptor-mediated effect, unrelated to ET-1-mediated mitogenic or melanogenic events, as it was replicated on melanocytes with no significant increase of cell proliferation as well as in melanocytes that lacked the ability to synthesize melanin. ET-1 treatment rescued melanocytes from UV-induced apoptosis as evidenced by reduced Annexin V staining and increased Bcl-2 levels. In addition, ET-1 promoted cell survival after UV irradiation through activation of the PI3K pathway. Inhibition of PI3K/Akt signaling attenuated the anti-apoptotic effect of ET-1 on irradiated melanocytes [46]. ET-1 was also demonstrated to be responsible for phosphorylation of Mitf, a helix-loop-helix transcription factor that is central to melanogenesis and survival of melanocytes [46]. Mitf phosphorylation is effected through ET-1-dependent activation of the mitogen-activated protein (MAP) kinases ERK1/2, which in turn phosphorylate the transcription factor CREB, upstream of Mitf [47, 48].

More importantly, when human epidermal keratinocytes were exposed to 6-hour UVB irradiation, a dual transcriptional response was observed involving upregulation of several apoptosis-related and DNA repair factors. TRAF-interacting protein (hTRIP), CD40 receptor-associated factor-1 (CRAF), cytotoxic ligand TRAIL receptor, death-associated protein kinase 1 (DAPK1) [49-51], but also ERCC1 (NER) and XRCC1 (BER) [52-54] were all found to be upregulated. These changes were in parallel with reduced expression of ET-2 at 6 h post-irradiation. Therefore, it might be that the final cellular fate after exposure to genotoxic stress by UV irradiation is determined by a balance between DNA repair and apoptotic processes, in both of which ET signaling seems to play a role [55].

Another important observation regarding the association between the ET axis and DNA repair is that ET-1 reduces UV-induced DNA photoproducts, thus implying an involvement of ET-1 in enhancement of NER. Therefore, ET-1 signaling not only exerts a proliferative and anti-apoptotic effect but also reduces accumulation of DNA damage, which is indispensable for maintenance of genomic health. The implication of pro-survival signals, other than the ET family, in DNA repair of keratinocytes has also been described for interleukin-12 (IL-12) and IGF-I which were both found to accelerate the removal of DNA photoproducts thus preventing UV-induced apoptosis in these cells [56, 57].

In addition to the direct DNA damaging effects of exposure to UV radiation, the latter is also a major source of reactive oxygen species (ROS) production that can secondarily cause oxidative DNA damage, as well as lipid peroxidation and protein damage [58]. Increased production of hydrogen peroxide, which is the main representative of ROS, following UV exposure was found to be reversed by ET-1 in human melanocytes. Thus, ET-1-mediated prevention of UV-induced oxidative stress indirectly contributes to prevention of oxidative DNA damage. Overall, activation of melanocortins and ET-1 signaling constitutes an indispensable cellular mechanism to overcome cancer-promoting effects of UV irradiation through reduced generation of hydrogen peroxide-mediated DNA damage and activation of DNA repair and melanogenesis pathways [46].

Accumulated evidence supports that melanoma patients have lower DNA repair capacity compared to the general population. Risk of melanoma was found to be increased by loss-of-function mutations in the melanocortin-1 receptor gene, indicating that inefficient or/and aberrant DNA repair is central to the development of melanoma. UV irradiation induces upregulation of various pro-survival signaling molecules including NGF, NT-3, MSH and ACTH, and ET-1. This upregulation seems to have a double effect on skin melanocytes. An early response involves inhibition of apoptotic signaling elicited by UV-induced DNA damage in melanocytes as well as enhancement of DNA photoproducts and oxidative stress metabolites, particularly hydrogen peroxide. According to the proposed model, exposure of the skin to UV radiation stimulates the activation of a MSH-, ACTH-, and ET-1-dependent paracrine network that promotes melanocyte survival, enhances the repair of cyclobutane pyrimidine dimers (CPD) and reduces the release of hydrogen peroxide. Collectively, these effects represent the immediate response to UV irradiation, which is followed by a delayed response of increased melanogenesis to establish photoprotection. Thus, melanocortins and ET-1 operate to maintain genomic stability of melanocytes and prevent evolution of unrepaired DNA damage to skin carcinogenesis [59].

There appears to be a direct association between ETRB signaling and expression of the BER member protein PARP-3. PARP-3 is part of a family of DNA damage surveillance factors [60]. ETRB antagonism was found to induce down-regulation of PARP-3 transcription in melanoma cell lines derived from primary tumors and metastases (cutaneous, lymph node, visceral) with the most prominent effect observed on the lines that were more sensitive to ETRB inhibition. Further, the extent of PARP-3 downregulation correlated with the level of apoptosis evidenced by histone-associated DNA fragmentation. The strongest decrease in PARP-3 expression in response to ETRB antagonism occurred in distal metastasis-derived cells, with little or no changes observed in primary tumor-derived melanoma cells [61].

A simplified schema of the role of ET axis in DNA damage response and repair in melanoma cells is depicted in Figure 2.

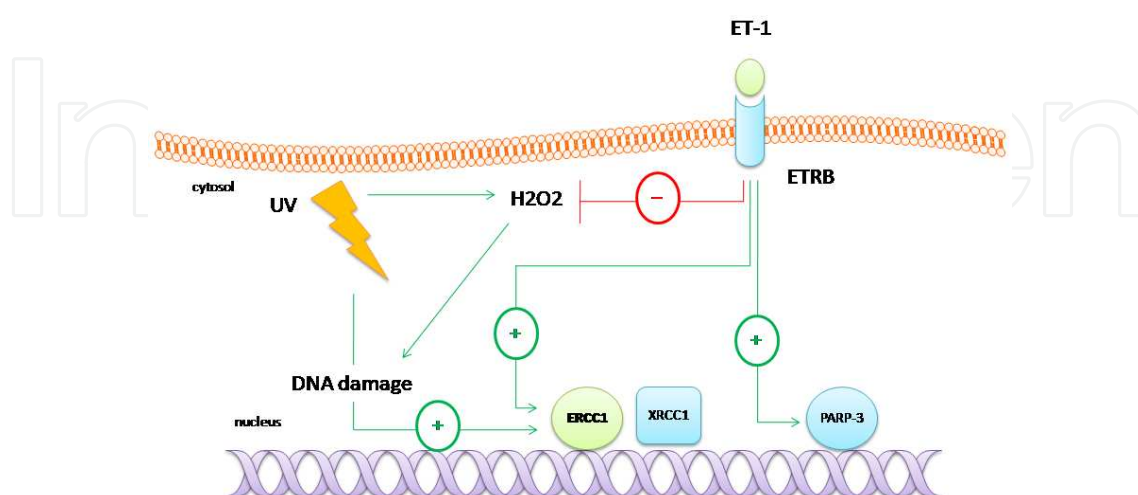


Figure 2. Simplified schema of the DNA damage control and repair transcriptional regulation by the ET axis in melanoma cells.

4. Conclusions

It is evident that the ET axis is greatly involved in the modulation of DNA repair processes. Elucidation of regulatory loops between ET family members and DNA repair factors at the transcriptional or/and post-translational level is a field of ongoing research. As expected, the use of existing or/and development of new targeted agents interfering with inhibition of ET signaling might be exploited either alone or in combination with chemotherapeutic drugs based on emerging mechanisms of action of the latter associated with DNA repair inhibition and sensitization of tumors to DNA damage.

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