Melanocyte UV resistance: Feelin’ the endothelin

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UV radiation is among the most important environmental carcinogens, abundant in sunshine and artificial tanning devices. UV is also among the most important causative factors for the development of melanoma, the most lethal of all UV-induced skin malignancies. Roughly 75 000 people in the United States alone are diagnosed with melanoma and nearly 10 000 die of the disease annually. UV mutations clearly contribute to the development of melanoma (1). In fact, the mutational burden of melanoma is among the very highest of all malignancies with an overrepresentation of UV signature mutations (2). Despite aggressive educational efforts to warn the public about the dangers of purposeful exposure to UV, recreational tanning is widespread and increasing in popularity. Although tremendous advances – most notably in immunotherapies and molecular targeting of the MAP kinase cascade – are being made in the treatment of advanced melanoma, the prognosis for the vast majority of patients with advanced disease remains dismal. The recent contribution by the Abdel-Malek group (3) is important because it informs us of how melanocytes cope with UV radiation and introduces a novel and potentially exploitable pathway for the prevention of melanoma. On the surface, it seems counter-intuitive that the efficiency whereby melanocytes resist or repair UV damage would not be in a continuous ‘optimal’ state of UV-readiness given their positioning in the skin. However, what has emerged through this report and others is that melanocytic UV resistance is regulated by paracrine factors, most notably, the MSH-MC1R-cAMP signalling cascade (4,5). The Abdel-Malek group now adds endothelin-1 (ET1) and endothelin B receptor (ETBR) signalling as a distinct means by which melanocytes protect themselves against UV damage.

Using primary human melanocytes, von Koschembahr (3) and colleagues found that pretreating melanocytes with ET1 prior to UV exposure decreased levels of photodimers in melanocytes. Protection by ET1 was observed even immediately after UV exposure, suggesting that ET1 may somehow ‘prime’ melanocytes from accumulating UV photodamage, even before repair can occur. However, the beneficial effects of ET1 were observed as long as 48 h after UV, raising the possibility that ETBR signalling may enhance the nucleotide excision repair (NER) pathway in some way. Importantly, ET1 treatment did not raise cAMP levels; therefore the ET1-ETBR signalling pathway does not simply rescue MC1R signals, and ET1 had no effect on the proliferation of melanocytes in the absence of cAMP-inducing factors. Melanin production was similarly unaffected in the time course presented, suggesting that reductions in UV burden are not simply explained by the UV-blocking effect by pigment. ET1 pretreatment decreased UV damage (as measured by cyclopentidine diomer load) by as much as 40% after UV damage and decreased UV-mediated apoptosis by even larger margins. Clearly, ET1 augments melanocytic resistance to UV injury.

ET1 treatment activated both JNK and p38 signalling as determined by their phosphorylation states and activation of ATF2, a downstream target of both. ET1-mediated ATF2 activation was calcium dependent because addition of the Ca2+ chelator BAPTA abrogated ET1-mediated JNK activation and ATF2 phosphorylation. ET-1-driven JNK-dependent ATF2 phosphorylation was confirmed in experiments using JNK inhibitors, and the importance of JNK in ET1-mediated melanocyte UV resistance was functionally confirmed by showing that JNK inhibition prevented ET1-mediated reductions in CPD’s and profoundly sensitized melanocytes to UV-mediated apoptosis. Of interest, p38 inhibition only marginally impaired ET1-mediated reductions in CPD load and had no effect on melanocyte UV sensitivity. Thus, although ET1-ETBR signals activate both the JNK and p38 pathways, the JNK cascade seems more relevant to melanocytic UV resistance.

With respect to possible links between ET1-ETBR signalling and NER, the authors found that ET1-accelerated clearance of XPC from foci of photodamage. Specifically, although XPC binding to UV-damaged foci was similar 3 h after UV, numbers of XPC-containing foci were less at 6 h in cells pretreated for 4 days with ET1. The investigators interpreted these data to indicate accelerated XPC function and detachment from NER complexes to allow repair to proceed; however, the data showed XPC disappearing entirely from some foci yet remaining just as bright (as untreated cells) in others rather than uniform diminished intensity throughout each of the foci as might be expected from accelerated clearance. Clearly, more mechanistic studies are needed to help clarify how ET1 impacts XPC function and NER efficiency.

Perhaps the most exciting aspect of the study is its translational implication for human melanoma prevention. Loss-of-function polymorphisms in MC1R correlate with a fair complexion, a tendency to burn rather than tan and most importantly an increased melanoma risk (6,7). Such UV-sensitive individuals accumulate more UV photodamage and mutagenesis in part because their melanocytes have blunted MC1R-mediated CAMP signalling and diminished NER. While attempts are being made...
to enhance skin pigmentation and UV resistance with skin-permeable MSH analogues, these therapies would not be expected to significantly people with homozygous MC1R signalling defects. Although the possibility remains to 'bypass' inherited MC1R defects with pharmacologic cAMP induction (8), the current work by the Abdel-Malek group introduces the ET1-ETBR cascade as an MC1R-independent mechanism to reduce UV burden in melanocytes, potentially of great benefit to the great numbers of melanoma-prone MC1R-defective individuals in the population.

These findings are intriguing at many levels. Most importantly, they introduce the possibility of minimizing melanocyte UV damage by pharmacologic manipulation of either ETRB signalling or relevant downstream signalling pathways such as JNK. Experimentally, many important questions remain as follows:

- How does ET1-ETBR signalling interact with the MC1R/cAMP pathway? Might ET1-ETBR signalling affect the recently identified cAMP-mediated PKA-ATR-XPA axis which is required for MC1R-enhanced NER (9)?
- How does ET1 enhance NER? Why does XPC disappear from some locations of photodamage in an accelerated manner yet linger at others?
- Since ET1-ETBR activated ERK, might this pathway somehow impact BRAF/NRAS – driven carcinogenesis? Alternatively, how might the presence of constitutively activated MAP kinase signalling (e.g. BRAF^{V600E}) affect the ET1 repair cascade?
- Might there be examples of melanoma predisposition based on defects in the ET1-ETRB signalling cascade as there are in MC1R defective individuals? In fact at least one study suggests this may be a possibility (10).

Together these exciting data advance our understanding of normal physiologic mechanisms by which melanocytes protect themselves against UV damage and open new areas of investigation in the attempt to minimize melanoma risk by enhancing melanocytic UV resistance.

Conflict of interest
The authors has no conflict of interests to declare.

References