Melanocyte growth is tightly controlled by a complex network of cell-cell communications and soluble growth factors. In situations where this delicate homeostasis is upset, the same melanocyte growth factors probably lead to the uncontrolled cell growth associated with melanoma. In this issue of the JID a paper by Stove and colleagues (2003) adds yet another member to the growing list of growth factors implicated in melanocyte control. The newest member of this ever-expanding family is the Heregulins (HRG), which are ligands for the 4–membered human epidermal growth factor receptor tyrosine kinase (RTK) family (also known as HER1-4 and ErbB1-4). The HER family of receptors is well known to cancer biologists as its members are often aberrantly overexpressed or mutated in a number of human tumors. Greater understanding of the HER/HRG system has led to therapeutic advances, with a humanized antibody (Herceptin, Genetech, San Francisco, CA) to the HER2 receptor being used to treat metastatic breast cancer.

Activation of the HER receptor follows ligand binding and the formation of either homo- or hetero-dimers; the components of which determine the strength of the signal generated. As a general rule, signaling from the homo-dimeric unit (such as HER2/HER2) is much weaker than a hetero-dimeric signaling unit (such as HER2/HER3). The reasons for the differential signaling of the homo- versus hetero-dimeric system are easily understood when it is considered that HER2 appears to lack any known ligand and HER3 is without intrinsic kinase activity (Yarden and Sliewkowski, 2001). Under physiological conditions, the HERs and their ligands mediate cell–cell interactions and are implicated in diverse responses ranging from cell division, motility, and adhesion to cell death (reviewed in Yarden and Sliewkowski, 2001). The HER/HRG system is also known to be involved in skin development and homeostasis, with knockout experiments revealing that HER1-null mice have poorly formed epidermis and hair follicles (Sibilia and Wagner, 1995; Threadgill et al., 1995).

The current study by Stove et al. was prompted by the observation that conditioned media from a melanoma cell line induced a strong phosphorylation of the HERs in MCF-7 mammary carcinoma cells. Following this initial observation, the authors found that HER2 and HER3 were expressed in a panel of melanocyte and melanoma cell lines. Western blotting also demonstrated the expression of HRG in 3 melanoma cell lines, with other melanoma and melanocyte cell lines showing limited HRG expression at the mRNA level only. One melanoma cell line in particular, called MJM, appeared to express mRNA for multiple isoforms of HRG, one of which was a novel form—which the authors named HRG24.

The authors also observed that the HRG expressing melanoma lines were able to secrete the functionally active HRG into the tissue culture media, which could then stimulate HER activity in MCF-7 cells. Having shown that HER2 and HER3 were expressed in melanoma cell lines and that HRG was released into the growth media, the authors went on to demonstrate the existence of a HRG autocrine loop in one of their melanoma cell lines. In this cell line, HER2 and HER3 were constitutively phosphorylated, indicating a level of basal activity. Prolonged treatment with the HER inhibitor, PD198393, led to concentration-dependent decreases in cell growth, indicating that HER activity was responsible for growth of this cell line. The sensitivity of the PD 198393 was confirmed by control experiments demonstrating that it had no antiproliferative activity in MCF-7 cells (which were also positive for HER2/3 – but did not produce HRG).

Activation of the HER/HRG system can also contribute to the constitutive MAP kinase activity of the cell line with a HER autocrine loop. This suggests that in addition to mutations (such as BRAF and N-Ras) and other growth factors (such as IGF-1 and bFGF) that the HER/HRG system can also contribute to the constitutive MAP kinase activity seen in melanoma cells (Satyamoorthy et al., 2003; Smalley, 2003).

A further interesting observation made is that the HER/HRG system can also be dysregulated in some of the melanoma cell lines, through a variety of means. Two of the melanoma cell lines tested lacked HER3 expression and were found to be unresponsive to recombinant HRG. Another of the melanoma cell lines was also unresponsive to HRG even though it expressed nonmutated forms of HER2 and HER3. The authors suggested that dysregulation of HER signaling in melanoma was a consequence of the tumor becoming growth factor-independent. It is also possible that the acquisition of activating mutations of BRAF, found in 66% of melanomas (Davies et al., 2002), would make the need for HRG signaling redundant. Indeed, it is further suggested by the authors that the down-regulation of RTKs during melanoma progression could be a mechanism for the nascent tumor to escape normal physiological control.

The authors also addressed a possible role of HRG in the growth of melanocytes. They were able to show that recombinant HRG stimulated HER phosphorylation in melanocytes, leading to increased cell growth. Furthermore, the enhanced growth was additive to that seen following basic fibroblast growth factor (bFGF) treatment. However, unlike bFGF, HRG was unable to promote melanocyte survival when seeded onto an apoptosis-inducing collagen gel. So it appears that whereas the HER/HRG system can promote melanocyte growth, there is little pro-survival activity. As melanocytes seem unable to produce their own HRG it is likely that any increased HER activity would be the result of paracrine HRG from either keratinocytes or fibroblasts. Indeed, there is some evidence to suggest that this HRG may be coming from keratinocytes, particularly as subconfluent keratinocytes do express HER1-3 and produce HRG in vitro (De Potter et al., 2001).

In summary, Stove and colleagues have identified a new and potentially important signaling system in melanocytes and mela-
noma. The role of this system in normal melanocyte physiology initially seems to be growth promoting, but other effects cannot be ruled out at this stage. The heterogeneous nature of melanoma is underscored by the fact that the HER/HRG system is at once required for growth in one melanoma line and functionally redundant in a number of others.

REFERENCES


