Wherefore Art Thou, YY1?

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In this issue, Taguchi *et al.* demonstrate that the transcription factor Yin Yang-1 (YY1) regulates proliferation in three-dimensional cultures of the HaCaT human keratinocyte cell line. HaCaT keratinocytes overexpressing YY1 form artificial epidermal constructs that are thicker than those produced from vector-transfected cells. RNA interference-mediated YY1 knockdown decreases the thickness of YY1-overexpressing constructs, indicating that YY1 mediates the thickening. In primary keratinocytes, overexpressed YY1 also inhibits differentiation marker expression induced by calcium, supporting the idea that YY1 is important in regulating epidermal structure and function.

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The transcription factor Yin Yang-1 (YY1) is so named because this protein was first identified as a factor that in the absence of adenoviral E1A repressed transcription of the adenoviral-associated viral promoter but in the presence of E1A activated its transcription (reviewed in Gordon *et al.*, 2006). YY1, a member of the zinc-finger Gli-Krüppel family of transcription factors, seems to be expressed ubiquitously and conserved from *Xenopus* to humans, with a series of eight splice variants of unknown function in humans (Gordon *et al.*, 2006). The *Drosophila* homolog of YY1 is pleiohomeotic, a member of the polycomb group family of homeotic gene repressors (Affar *et al.*, 2006). YY1 is reported to regulate the expression of various genes (Gordon *et al.*, 2006; Shi *et al.*, 1997), in some cases activating and in others repressing gene transcription. Several models have been proposed to explain the mechanism by which YY1 exerts these effects; in many cases YY1 appears to interact directly with components of the transcription machinery and/or other transcription factors (Gordon *et al.*, 2006).

In mice, a global lack of the YY1 gene results in embryonic (peri-implantation) lethality. Interestingly, Shi and colleagues used a combination of hypomorphic and floxed alleles to generate animals expressing 25, 50, or 75% of the normal amount of YY1 protein (Affar *et al.*, 2006). These investigators demonstrated dosage-dependent effects of YY1 gene/protein expression on embryogenesis, with about one half of the embryos having a YY1 level 25% of that of wild-type mice dying during late fetal development. The mice that survived until parturition weighed less than wild-type littermates (approximately 80% of the weight of the wild-type animals), appeared pale and slightly cyanotic, and died within a day of birth. Necropsies revealed that the lungs failed to inflate in these animals. The possibility of a skin phenotype was not investigated, although it is tempting to speculate, particularly in view of the work presented by Taguchi *et al.* in this issue, that closer examination might reveal epidermal abnormalities as well. In future studies, this floxed YY1 mouse model may prove useful in determining the role of YY1 in epidermal structure and function.

YY1 has been reported to regulate cell cycle progression: a decrease in levels of YY1 using a hypomorphic allele as described above, ablation of a floxed gene by Cre recombinase, or RNA interference-mediated knockdown leads to a reduction in proliferation in mouse embryo fibroblasts and cervical carcinoma (HeLa) cells (Affar *et al.*, 2010). Indeed, complete loss of the gene appears to block cytokinesis, and microarray analyses of reduced (25%) YY1-expressing compared with wild-type mouse embryo fibroblasts revealed an upregulation of 231 genes and a decrease in 293 genes (Affar *et al.*, 2006), many of which are known to be involved in modulating growth. Consistent with these findings, Taguchi *et al.* (2011) demonstrate that overexpression of full-length YY1 in HaCaT human epidermal keratinocytes induces proliferation and results in a thickening of an artificial epidermis reconstituted from these cells. In addition, YY1 overexpression suppresses expression of several differentiation markers, including keratins 1 and 10, involucrin, and filaggrin, supporting YY1's reported ability to repress the promoter activity of the differentiation markers involucrin (Alvarez-Salas *et al.*, 2005) and loricrin (Xu *et al.*, 2004). It should be noted that the investigators use the HaCaT cell line, a spontaneously immortalized keratinocyte cell line generated from adult human skin under conditions of low calcium (0.2 mM)-containing medium and elevated temperature (38.5 °C). The HaCaT cells do not recapitulate normal differentiation entirely, in that the cells express differentiation markers but at the same time continue to proliferate in high-calcium medium (Boukamp *et al.*, 1988). (Taguchi *et al.* also note a lack of loricrin immunoreactivity in the HaCaT-derived artificial epidermis.) Nevertheless, the results were replicated in two-dimensional primary cultures of mouse epidermal keratinocytes, in which overexpression of YY1 inhibited the elevated extracellular calcium concentration-induced expression of several differentiation markers (keratin 1, involucrin, and loricrin; Taguchi *et al.*, 2011). Accordingly, the importance of YY1 in regulating epidermal keratinocyte function does not appear to be limited to a single species or to immortalized keratinocytes.

A second caveat is that the artificial epidermal constructs used in this study

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were derived from a clonal population of YY1-overexpressing keratinocytes (Taguchi *et al.*, 2011). It remains possible that any observed differences in

> The transcription factor YY1 regulates proliferation by keratinocytes as well as epidermal structure.

proliferation and/or thickness result from clonal variations rather than from overexpression of YY1. However, this concern is largely obviated by the results obtained with RNA interference. Thus, lentiviral short hairpin RNA-mediated knockdown of the overexpressed YY1 returns the artificial epidermis to a thickness similar to that of the control, and differentiation markers are re-expressed, suggesting that the differences observed are, in fact, due to overexpressed YY1, and providing evidence that YY1 promotes proliferation and inhibits differentiation of epidermal keratinocytes.

A question that remains is whether YY1 is related to human skin disease. Accumulating evidence supports a role for YY1 in several human cancers, including various epithelial malignancies such as prostate, ovarian, breast, cervical, colon, and lung cancers (Castellano *et al.*, 2009). Other members of the Gli-Krüppel family of transcription factors (e.g., Gli1 and Gli2) are involved in the development of several skin tumors, including basal cell carcinoma, basaloid follicular hamartoma, cylindroma, and trichoblastoma (Sheng *et al.*, 2002), and Gli-similar 1 (Glis1) expression is upregulated in psoriasis (Nakashani *et al.*, 2006). Finally, Kawada *et al.* have demonstrated that YY1 functions with another transcription factor, Sp1, to transactivate the gene *ATP2C1*, which encodes for a Golgi-localized calcium ATPase (Kawada *et al.*, 2005). Mutations in this gene and/or loss of protein expression result in Hailey–Hailey disease, an autosomal dominant blistering skin disease characterized by insufficient cell–cell adhesion among suprabasal keratinocytes. Because YY1, together with Sp1, increases the expression of *ATP2C1*, it seems possible that congenital deficiency of YY1 may contribute to the etiology of Hailey–Hailey disease in some patients. Therefore, additional studies are warranted in order to define the role and mechanism of action of YY1 in regulating keratinocyte structure and function.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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Eczema across the World: The Missing Piece of the Jigsaw Revealed

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Cleverly using records obtained from the 2003 National Survey of Children's Health (NSCH), Shaw *et al.* provide a pioneering glimpse into the burden of eczema across the United States. Using parental reports of a doctor's diagnosis of eczema in the past 12 months, the authors show that eczema affects around 9–18% of children age 17 and under. The study confirms reported associations such as living in metropolitan areas, higher household education level, and black ethnicity. Novel findings include the demonstration of higher eczema prevalence along the East Coast. The study correlates well with previous reports and may help point to environmental factors that contribute to the development of eczema.

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One of the most striking features about world maps of eczema (atopic dermatitis) prevalence derived from the International Study of Asthma and Allergies in Childhood (ISAAC), which involved more than 1 million children from 230 centers in 97 countries (Figure 1), is the almost complete absence of data from the

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