

In this issue of *The Journal*, Varani and co-workers (1) report that all-trans retinoic acid (RA) produces in organ-cultured human skin specimens and in conventional monolayer cultures of skin-derived cells the same histologic and biochemical changes previously observed in RA-treated photoaged skin in vivo; and, more surprisingly, that these changes occur comparably in sun-protected intrinsically aged skin and in sun-exposed photoaged skin, whereas different effects are observed in neonatal skin. This beneficial effect of RA in intrinsically aged skin confirms and expands the recent clinical observation of Kligman and co-workers (2) that topical application of RA 0.025% cream, versus vehicle control cream, daily for nine months to the inner thigh of women aged 68–79 years strikingly improved the skin's histologic appearance, reversing changes associated with intrinsic aging. The improvements included epidermal thickening, reconstitution of rete pegs, and deposition of new dermal matrix materials. Both Varani et al. and Kligman et al. conclude that RA affects not only photodamage, but the consequences of aging itself. Is aging truly reversible? If so, by what mechanism does RA produce this reversal?

Aging is a basic biologic process that over time renders organisms progressively less able to respond to their environment and thus more vulnerable to injury and disease (3). By most definitions, aging begins in early adulthood, as development ends, and is at least to a large degree under genetic control. Aging may also be viewed as the latter stages of the same genetic program that governs embryonic and postnatal development, equivalent at the cellular level to progressive differentiation. In this intellectual framework, it is of interest that RA is among the best documented embryologic morphogens (4, 5) and has well recognized roles in the development and postnatal maintenance of many tissues throughout the body, certainly including the skin (6). Moreover, a wide variety of otherwise apparently contradictory effects of RA in vivo and in vitro can be viewed as an ability of this molecule to "normalize" cellular behaviors, rather than specifically to stimulate or inhibit them (6).

Appreciation of RA's central role in embryogenesis and tissue homeostasis was greatly expanded by the discovery that its effects are mediated through binding to nuclear retinoic acid receptors (7, 8), members of a super family of nuclear receptors for steroid hormones and protein growth factors, highly conserved throughout evolution, that upon ligand binding function as transactivating elements to modulate gene transcription directly. The extremely tight regulation of circulating RA levels in serum, the profound teratogenic effects of even transient RA elevations during embryogenesis, and the complex array of serum, cytoplasmic, and nuclear binding proteins that modulate retinoid access to RA response elements in the genome (6–9) all testify to the biologic importance of this molecule. Unfortunately, the impact of aging on RA nuclear availability or, conversely, of RA nuclear availability on the aging program, is virtually unknown. Might aging represent in part an end organ

insensitivity to RA, surmountable by administration of RA in pharmacologic amounts? In the present study (1) the authors compare the effect of 3 μ M RA, a dose comparable with that measured in RA-treated skin in vivo (10), to the complete absence of RA in their cultures. The effect of age on serum levels, estimated at 1–2 μ M (11), let alone tissue or nuclear concentrations, is unknown. Dose–response curves for RA effects in both young and old organ cultures would surely be of interest.

In the absence of a precise molecular definition of aging, it is impossible to determine whether the aging process has truly been reversed or whether changes observed after an intervention simply counterbalance those produced by aging. However, this ambiguity does not diminish the clinical utility of such changes. In the skin, RA treatment has been reported to reverse the epidermal atrophy associated with both aging and photoaging (12–16) and to stimulate new collagen deposition in the papillary dermis (17), with concomitant improvement in the appearance of skin in controlled clinical trials (12–15). The present organ culture results (1) confirm these in vivo findings, and suggest that the RA effects are mediated at the cellular level through enhanced protein production and cell growth rate.

It is tempting to speculate that RA might find clinical applications beyond the treatment of cosmetically displeasing aged skin, for example in stimulation of wound healing in older persons, as has already been suggested in small uncontrolled trials. Similarly, considerable data supports the possibility of prophylactic treatment for cancer-prone skin and mucous membranes to reduce the rate of carcinogenesis (6, 18–22), known to increase exponentially with age (18). Studies of possible effects on age-associated dysfunction in other retinoid-responsive tissues would also be of great interest. The ever increasing number of frail elderly in our society (23) surely mandates every effort to turn back the clock for pathology-prone organ systems.

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