

# Retinoids and Retinoic Acid Treatment of Skin Aging

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This chapter will give a short overview of the effects of biology of retinoids and their benefits on the signs of skin aging. Skin aging, which is reviewed much more extensively in previous chapters, is a complex process associated with changes in skin ultrastructure, biochemistry and function. These changes are a consequence of chronological (intrinsic) aging which is further exacerbated by irradiation, mainly UV irradiation, leading to photoaging or external aging. Superimposed on these effects are influences from lifestyle factors such as habits, diets, smoking, or diseased states (e.g. diabetes) and the effect of gravity. Reductions in endogenous hormone levels can also contribute to the aging process for example during menopause (e.g. reduced concentrations of estrogens). The clinical changes to skin associated with photoaging are age spots (freckles or ephelides, solar lentigines and solar keratoses) and wrinkles (**Figure 7.1**).<sup>1</sup>

The main biological changes occurring in facial wrinkles were described by Varlet et al.<sup>2</sup>, Contet-Audonneau et al.<sup>3</sup> and Green et al.<sup>4</sup> The first two groups identified alterations in the extracellular matrix components. The dermoepidermal junction (DEJ) was modified by a decrease in the levels of collagen IV and VII combined with fewer oxytalan fibers under the wrinkles. Chondroitin sulfate levels also decreased combined with an asymmetrical variation of glycosaminoglycan GAG deposition on both sides of the wrinkles. A distinct diminution of oxytalan elastic fibers and fibrillin occurred as has also been reported for photodamaged forearms by Watson et al.<sup>5</sup> However, Green et al.<sup>4</sup> (**Figure 7.2**) established that a thinning



**Figure 7.1.** Photographs of two ladies, one from Chicago (a) and a farm worker from Michigan (b). Both are 71 years old. Notice the extensive photo damage on the face of the farm worker (b). Courtesy of Professor CEM Griffiths, University Of Manchester, Hope Hospital.

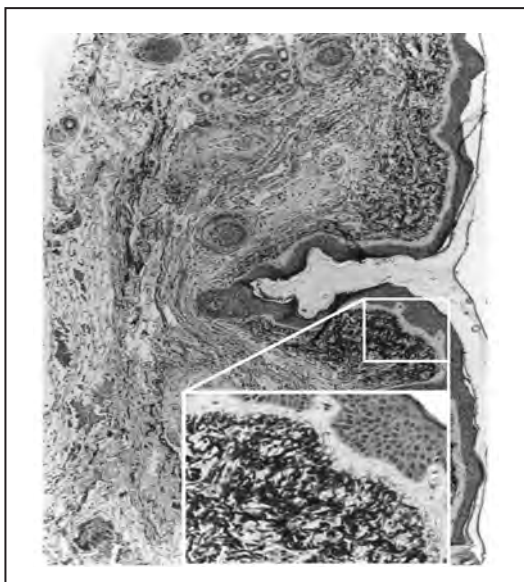
and compression of the epidermis occurred at the wrinkle base with marked asymmetrical changes in matrix composition. Apparently, the collagen network was aligned around the wrinkle with “scar” like collagen under the wrinkle and a relatively photoprotected elastic network at the base of the wrinkle. The wrinkles also appeared to be under compression in their upper walls. Such tensional forces affect fibroblast alignment and collagen synthesis patterns. Underneath the wrinkle the connective tissue shows distinctive evidence of an aligned matrix perpendicular across the wrinkle. The microscar extends well beyond the visible wrinkle and may be involved in maintaining tension in the surrounding skin. Elastosis also showed asymmetry with greater amounts in the lower face of the wrinkle but the deeper areas of the wrinkle had less. At the wrinkle base, collagen and biglycan were not synthesized but levels of chondroitin-4-sulfate showed a slight increase. All of this evidence indicates that significant remodeling of deeper collagen structures to reduce axial stiffness and new matrix production is necessary to lead to wrinkle effacement. The skin can repair some of UVR-induced damage provided that UVR exposure is avoided or reduced<sup>6</sup> but the most

effective route is through intervention, especially with retinoids (**Figure 7.3**), which is the subject of this chapter.

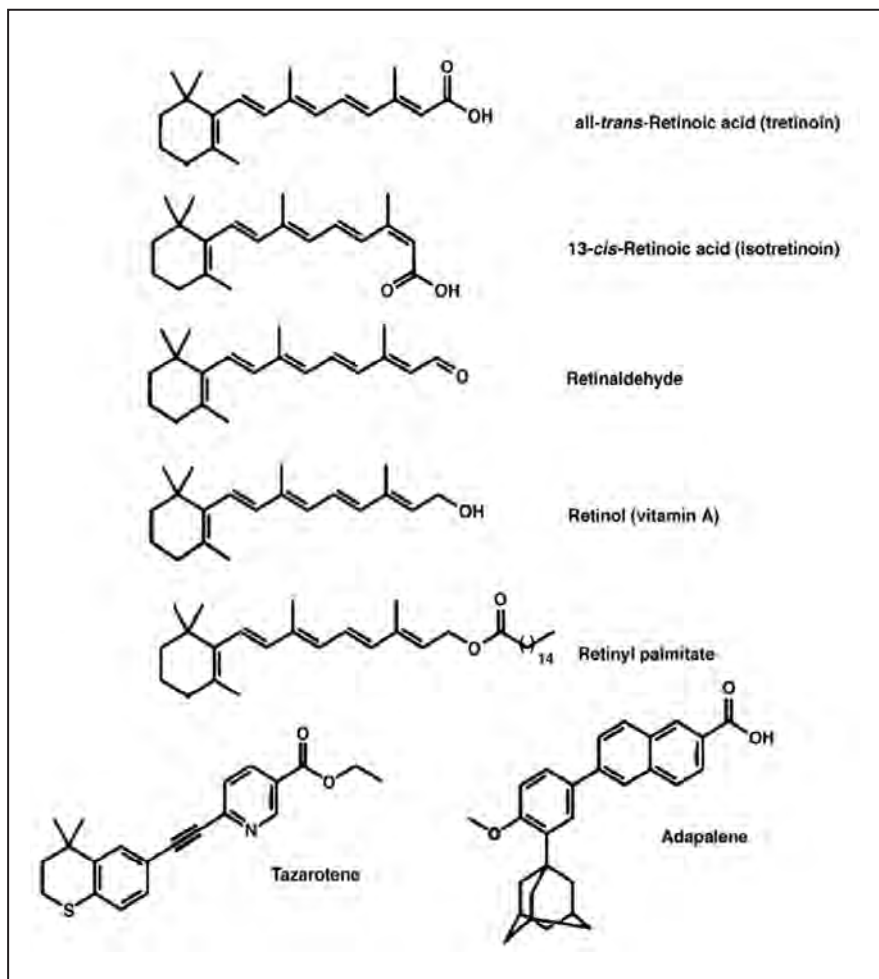
## Nuclear hormone receptors and the retinoid receptors

Nuclear hormone receptors exert their effects directly on genes by binding to DNA in the nucleus, not least being the retinoid receptors. They are composed of

multiple functional domains. The N-terminal A and B domains contain isoform-specific ligand-independent transactivation functional domains: AF-1. The DNA binding domain (C or DBD) is highly conserved and contains two zinc-binding motifs responsible for the recognition of the nuclear hormone response element located in the promoter region of target genes. The E domain is the ligand binding domain (LBD) and is responsible for the dimerization of the receptors, ligand-dependent transcriptional activation functions (AF-2) and translocation to the nucleus (**Figure 7.4**).<sup>7</sup> The C-terminal domain is also involved in interactions with other transcription factors, enzymes and co-regulators. However, in the nucleus all receptors interact with the response elements of the target genes. These DNA sequences consist of six base pairs in single units or in tandems with a base pair spaced between the hexamers (half sites). The orientation of the hexamers as direct repeats, palindromes or inverted palindromes and the number of nucleotides acting as spacers dictates the specificity of binding.



**Figure 7.2.** Stained wrinkle section perpendicular to the long axis of the wrinkle displayed in the correct orientation. Aligned collagen can be seen at the base of the wrinkle whereas elastotic deposits are visible on the lower aspect of the wrinkle and absent from the base. Courtesy of Dr Martin Green, Unilever Research, UK.<sup>4</sup>



**Figure 7.3.** Typical structures of retinoids.

Two classes of nuclear receptors mediate the action of endogenous retinoids.<sup>7</sup> Both types of receptors are composed of three subtypes (alpha, beta and gamma).<sup>8</sup> As described above, the nucleotide spacer dictates binding of homo- or heterodimers of nuclear receptors. The simplest is the DR-1 of the RXR-RXR homodimer; the retinoic acid response element (RARE; AGGTCA). However, the polarity of binding to the response element is reversed in these receptors with the RXR's occupying the 5' half site when coupled to the RAR.<sup>9</sup> The RAR DR is 1, 2 or 5 (DR1, DR2, DR5) depending if its RAR alpha, beta or gamma isoform.

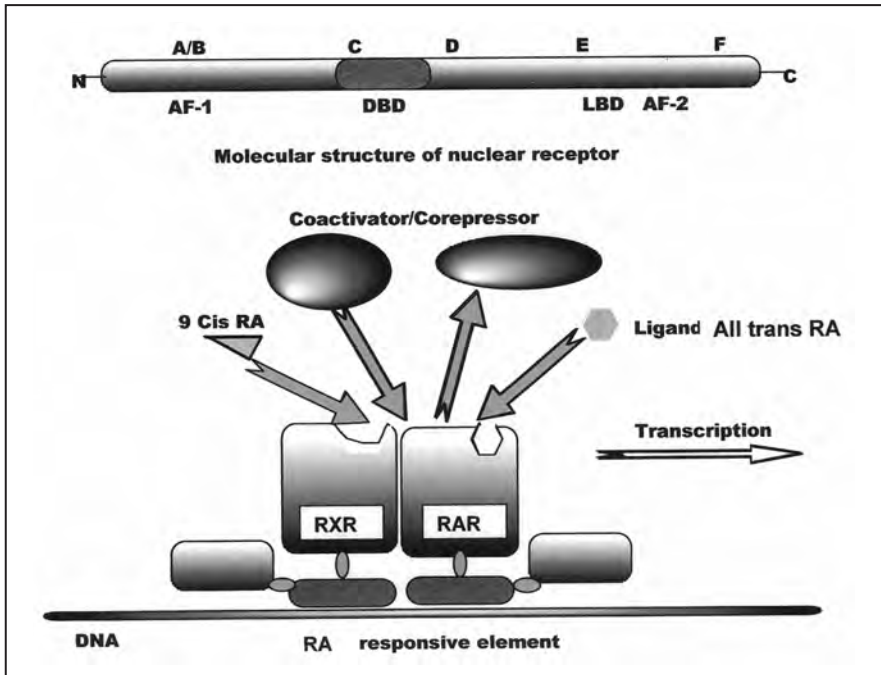


Figure 7.4. Molecular structure of a nuclear receptor.

The pleiotropic effects of retinoids are due to the existence of multiple RA receptor isoforms and as a result of the different combinations of RAR-RXR heterodimers. RARs and RXRs mainly act as heterodimers on binding to the RAREs. The RARs can be activated by binding all-trans retinoic acid (atRA) or 9cisRA, however, of the different retinoids RXRs can only be activated by 9cisRA. The RXRs predominate in human skin especially RXR $\alpha$ . The concentration of RXRs is five times as high as that of the total concentration of RARs. Of the RARs 87% is gamma and 13% alpha. Only small amounts of RAR beta are found in dermal cells and melanocytes. Human sebocytes *in vitro* also express mRNA or RAR alpha and gamma together with RXR alpha. Although both atRA and 9cRA bind RAR *in vitro*, RAR gamma preferentially binds atRA. Both 9cRA and 13cRA can be isomerized to atRA. The isomerization of 9cRA has been reported to occur in keratinocytes.<sup>8</sup>

The ligand binding pockets of nuclear receptors have been determined by X-ray crystallography.<sup>10</sup> This domain consists of a series of alpha helices that give rise to a novel anti-parallel alpha-helical