# Review of Retinoid Biology: Part 1

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## Retinoid Receptors (Brand names)

<table>
<thead>
<tr>
<th>Retinoid receptors:</th>
<th>Definitions</th>
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<tbody>
<tr>
<td>Retinoid X receptor a is key partner in heterodimers with RAR, Vit D, thyroid, and PPAR (peroxisome proliferator activator receptors)</td>
<td>RAR-γ (87%) &gt; RAR-α (13%) &gt; RAR-b (minimally detectable)</td>
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<tr>
<td>Retinoid receptors:</td>
<td>RXR α (90%) &gt; RXR-β &gt; RXR-γ (not detectable)</td>
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<tr>
<td>Natural ligands</td>
<td>Human epidermis is regulated by RXR-α and RAR-γ heterodimers</td>
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<tr>
<td>RAR- all trans retinoic acid</td>
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<td>RXR- 9-cis retinoic acid</td>
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</table>

## First generation retinoids:

- Tretinoin (Retin-A most common; many other brand name formulations available)
- Isotretinoin (Brands available in the US: Claravis, Amnesteem, Absorica, Myorisan, Zenatane)
- Retinol (numerous OTC products)
- Retinaldehyde (numerous OTC products)

- Tretinoin (all-trans-retinoic acid) binds to all RAR receptors; a naturally occurring metabolite of retinol; photo-unstable and may be oxidized by benzoyl peroxide
- Isotretinoin does not bind to retinoid receptors: metabolized to tretinoin
- Oral bioavailability of isotretinoin increased with fatty foods
- Retinol AKA Vitamin A, precursor of retinoic acid
- Retinaldehyde is a precursor of retinoic acid; may be as effective as tretinoin and better tolerated (per small studies)

## Second generation retinoids:

- Etretinate (Tegison)
- Acitretin (Soriatane, Neotigason)

- Etretinate is lipophilic: deposited and stored in fatty tissue for several years
- In the presence of alcohol, acitretin is re-esterified to etretinate, resulting in prolonged storage and teratogenicity

## Third generation retinoids (polyaromatic compounds, AKA arotinoids):

- Bexarotene (Targretin)
- Tazarotene (Tazorac, Fabior, Avage, Zorac)
- Adapalene (Differin)

- Bexarotene is a synthetic retinoid analog that selectively activates only retinoid X receptors. Associated with central hypothyroidism (decreased TSH, decreased T4)
- Tazarotene is the first of a new generation of receptor-selective retinoids targeting RAR-β and RAR-γ (results in decreased Tsg1, K6, K16, EGF)
- Adapalene’s primary target is RAR-γ, light stable, highly lipophilic

## Retinoid responsive gene / gene products

| Retinoids block UV induction of c-Jun | c-Jun and c-Fos are components of the AP-1 transcription factor |
| Rate limiting enzyme in phospholipase C pathway | Phospholipase C polyamines (pro-inflammatory) |
| May be important in treatment of acne | |
| Increase TH1 cytokines and decrease TH2 cytokines | Increase IL-12 and IFN-gamma (anti-neoplastic cytokines) |
| Increase cell mediated cytotoxicity and stimulate NK-cell activity | |

## Retinoid effects in CTCL

- Increase IL-12 and IFN-gamma (anti-neoplastic cytokines)
- Increase cell mediated cytotoxicity and stimulate NK-cell activity

## Retinoid effects in photoaging

- Thinning of the stratum corneum
- Thickening of nucleated epidermis, promotes differentiation, increased keratohyaline granules, Odland body secretion, increased filagrin
- Increased collagen I fibers in the dermis
- Decreased matrix metalloproteinases
- Increased papillary dermis elastic fibers
- Increased production of hyaluronic acid and fibronectin

## Retinoids effects in psoriasis (pustular/erythrodermic/palmoplantar)

- Acitretin and isotretinoin are effective in inducing desquamation but only moderately effective in clearing psoriatic plaques. Highly effective when combined with 311-nm UVB or PUVA (called re-PUVA).