Review of Retinoid Biology: Part 1

Mariana Phillips, MD. (Updated July 2015)*

Retinioid Receptors (Brand names)	Definitions
Retinoid receptors: Retinoid X receptor a is key partner in heterodimers with RAR, Vit D, thyroid, and PPAR (peroxisome proliferator activator receptors	RAR-γ (87%) > RAR-α (13%) > RAR-b (minimally detectable) RXR α (90%) > RXR-β > RXR-γ (not detectable) Human epidermis is regulated by RXR-α and RAR-γ heterodimers Natural ligands RAR- all trans retinoic acid RXR- 9-cis retinoic acid
First generation retinoids: Tretinoin (Retin-A most common; many other brand name formulations available)	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 (Brands available in the US: Claravis, Amnesteem, Absorica, Myorisan, Zenatane)	Isotretinoin does not bind to retinoid receptors: metabolized to tretinoin Oral bioavailability of isotretinoin increased with fatty foods
Retinol (numerous OTC products)	Retinol AKA Vitamin A, precursor of retinoic acid
Retinaldehyde (numerous OTC products)	Retinaldehyde is a precursor of retinoic acid; may be as effective as tretinoin and better tolerated (per small studies)
Second generation retinoids: Etretinate (Tegison)	Etretinate is lipophilic: deposited and stored in fatty tissue for several years
Acitretin (Soriatane, Neotigason)	In the presence of alcohol, acitretin is re-esterfied to etretinate, resulting in prolonged storage and teratogenicity
Third generation retinoids (polyaromatic compounds, AKA arotinoids): Bexarotene (Targretin)	Bexarotene is a synthetic retinoid analog that selectively activates only retinoid X receptors. Associated with central hypothyroidism (decreased TSH, decreased T4)
Tazarotene (Tazorac, Fabior, Avage, Zorac)	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 (Differin)	Adapalene's primary target is RAR-γ, light stable, highly lipophilic

Retinoid responsive gene / gene products	Effect
Inhibits homeobox proteins, regulatory transcription factors	Responsible for body axis formation, patterning, limb formation, and other crucial processes during development- TERATOGENICITY
Retinoids block UV induction of c-Jun	c-Jun and c-Fos are components of the AP-1 transcription factor
Retinoids repress the activity of transcription factors AP1 and NF-kappa-β	Inhibition of AP-1 results in potent anti-proliferative and anti-inflammatory properties and decreases matrix metalloproteinase synthesis Reduced NF-kappa-β results in decreased pro-inflammatory cytokines (TNF-α, IL-1, IL-6, and IL-8)
Retinoids inhibit ornithine decarboxylase	Rate limiting enzyme in phospholipase C pathway Phospholipase C polyamines (pro-inflammatory)
Retinoids inhibit toll like receptor-2 (TLR-2)	May be important in treatment of acne
Retinoid effects in CTCL	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 photoaging	Thinning of the stratum corneum Thickening of nucleated epidermis, promotes differentiation, increased keratohyaline granules, Odland body secretion, increased fillagrin 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/ palmaplantar)	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).

Mariana Phillips, M.D., is currently an assistant professor at the Virginia Commonwealth University in Richmond, Virginia

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***Reviewed and updated July 2015 by: Alina Goldenberg, MD, Emily deGolian, MD, and Sharon Jacob, MD.**