A previous article on the use of Retin-A™ (topical tretinoin) for the treatment of sun damaged skin, described evidence that Retin-A™ was an effective agent for increasing the mitotic activity of surface skin cells, increasing the turnover of follicular epithelial cells, which was of interest primarily in the treatment of acne, and increasing the amount of collagen in the reticular layer of the dermis. However, the mode of action for tretinoin was unknown. A great deal has now been learned about the structural and molecular changes that can be induced by Retin-A™ that account for the numerous clinical benefits achieved by this agent. In this article, I would like to take a new look at topical tretinoin, its place in skin treatment today, and its mode of action.

The role of long-term exposure to the ultraviolet rays of the sun in skin damage is well-documented. Both UVA and UVB have been implicated in producing chronic cumulative changes in skin. In addition, chronological aging can damage skin. Most dermatologists believe that photo-aging does more damage than chronological aging. For the most part sun damaged skin, which typically displays deep wrinkles, and thickening and cracking of the stratum corneum with accompanying flaking and scaling, is seen superimposed over the sagging and fine wrinkling associated with chronological aging. Benign epidermal growths such as seborrheic keratoses (scaling plaques), precancerous actinic (from sun damage) keratoses, and the more serious basal cell, squamous cell, and melanoma skin cancers, have been linked in many studies to long term exposure to ultraviolet radiation. A major skin alteration seen in histological examination of tissue is the accumulation of elastic fibers in the papillary region of the dermis, a condition known as solar elastosis. It is believed that solar elastosis gradually replaces normal collagen tissue in the papillary region. This greatly changes the architecture of sun damaged skin over time.

The most serious photodamage is believed to result from direct damage to the DNA of skin cells. The response to this damage is pyrimidine dimers that can cause a variety of mutations in sun damaged skin. Following chronic exposure to UV light, changes may be seen in the elastin, collagen, papillary dermis, reticular dermis, and lymphocytes of the skin. Elastin tends to completely degenerate into amorphous masses, and these thickened, ineffective masses of elastin fibers proliferate in the dermis. There is a marked decrease in both collagen fibers and collagen bundles in the dermis.

In the papillary region of the dermis, there is a loss of small blood vessels, which are replaced by abnormal, highly visible capillaries known as telangiectatic capillaries. Fibroblasts and mast cells increase in the reticular region of the dermis, an increase in chronic inflammation is evidenced by an increase in cellularity in that region. The number of lymphocytes and Langerhans cells in the dermis is markedly decreased.

There are many topical preparations on the market today for the treatment of skin damaged by the environment, e.g. ultraviolet radiation, smoking, wind and chemical exposure, and skin damaged by chronological aging. These treatments include the retinoids, derivatives of vitamin A (i.e. Retin-A™), which are the most studied group and the most commonly used series of treatments for photodamaged skin. In 1996, the Food and Drug Administration approved Renova™, which is an emollient form of tretinoin, specifically for the treatment of the aging face. Glycolic acid and lactic acid are the alpha-hydroxy acids most commonly found in skin treatment products. Salicylic acid, a beta-hydroxy acid, is currently under investigation to determine its overall effectiveness in skin treatment. Other agents being studied include vitamin C, vitamin K, and topical hormone treatments.

A closer look at the most recent studies of tretinoin shows in both clinical and histological evidence that some of the effects of photo-damage in skin can be reversed with this product. Among the structural improvements are normalization of the atypical cells of the epidermis including increased numbers of mitochondria, ribosomes, and endoplasmic reticula. The studies also noted are enhanced survival of keratinocytes, effects of anti-inflammation, deposition of new dermal collagen and, very importantly, formation of new blood vessels. This formation of new blood vessels not only improves the color of aging or damaged skin but also improves the flow of nutrients to the treated skin, giving it a much needed boost in the repair process. Stimulation of epidermal cell turnover causes keratinocytes to be more quickly removed from the stratum corneum, which improves the texture of the skin surface. Accumulated melanin in the basal layer, which causes “old age spots” is transported and shed, which tends to even out the overall pigmentation of the skin.

The history of tretinoin is an interesting one. In the late 1960’s researchers at the University of Pennsylvania discovered that...
tretinoin was useful in treating acne. However because the early formulations of tretinoin were fairly irritating and had a lightening effect on darker skin tones. Thus dermatologists did not initially accept tretinoin. It was not until the 1970’s that the potential for treatment of photo-damaged skin with tretinoin was recognized and investigation into this possibility got underway. One factor that prompted research in this area was that female patients being treated with tretinoin for acne were indicating to doctors that their skin looked better overall (i.e. smoother and less wrinkled with less blotchiness) as their acne improved.6

In 1986, Dr. A.M. Kligman and his associates at the University of Pennsylvania released the first results of their studies on photodamaged skin. These studies demonstrated that topical tretinoin could produce a smoother, less wrinkled and less pigmented appearance to the skin after only a few months of treatment. These original studies were not controlled, but did include a great deal of histological evidence to document their claims. Since that time many controlled clinical and histological studies have been done that have confirmed and extended the original studies. The results of these studies culminated in the historic FDA decision to approve tretinoin for treatment of aging skin in addition to its use as an acne treatment product.6

Today we know that retinoids such as tretinoin can regulate genes in two distinct ways by means of well-documented retinoid receptors in cell nuclei.5 Two classes of receptors have been identified so far: retinoic acid receptors (RARs) and retinoid X receptors (RXRs). RARs bind both all-trans-retinoic acid and 9-cis-retinoic acid (two clinically useful retinoids), whereas RXRs bind 9-cis-retinoic acid but not all-trans-retinoic acid. The distinction is important in the formulation of synthetic retinoids since the response to retinoids depends on the type of receptor that is targeted by the treatment agent. Cellular response is thought to be very complex, most probably the result of a cascade of gene activation. Since their discovery, the nuclear receptors for retinoids have been grouped together with steroid hormone receptors on the basis of their similar mechanism of action. One way that retinoids regulate genes is to activate transcription by binding to ligand-dependent retinoid receptors. Binding of the retinoid causes a shape change which exposes a DNA binding site on the receptor. The activated receptor then controls cell function by stimulating the expression of specific genes. Alternately, retinoids can suppress other transcription factors.5

This knowledge, though far from being completely researched, is an area of investigation today, not only for skin care treatments but also for cancer research. For instance, some of the skin damage caused by UV light results in the breakdown of collagen in the dermis, which is followed by the tissue’s imperfect attempt at repair. Ultraviolet light activates a series of phosphokinases which, in turn, activate c-Fos and c-Jun genes that activate the AP-1 transcription factor. AP-1 then causes the activation of several proteinases including collagenase, gelatinase, and stromatolysis, all of which contribute to the breakdown of collagen.5 Recent research6 indicates that tretinoin results in a 70% inhibition of AP-1 binding to DNA resulting in there is a significant reduction in proteinase activation. Based on this evidence, it is thought that tretinoin may actually be able to reduce photodamage to skin as well as to enhance tissue repair.6

With respect to photodamaged skin, the most severely damaged skin (rough scaling surface and mottled appearance) appears to display the greatest improvement following to tretinoin treatment.4 Greatest clinical improvement is also related to the concentration and frequency of tretinoin used. Topical formulations of tretinoin are available, by prescription only, in strengths of 0.025%, 0.05%, and 0.1% Renova’.7 The treatment approved by the FDA for the treatment of aging skin is a 0.05% emollient cream which seems to be well tolerated by users and is preferred by most users.8 Sometimes treatment is started at the lowest possible dose until the person’s skin adjusts, and then concentrations are increased to the highest tolerated dose for that person.

The product insert indicates that sensitive individuals may experience some skin redness, swelling, or temporary crusting. However, the clinical response does not correlate with the magnitude of skin irritation that takes place with the treatment, which means that the improvement is not just a result of chronic irritation of the skin surface.8

People who use tretinoin for damaged skin can usually expect to see smoothing of surface roughness in one to two weeks. The skin takes on a rosy glow, as a result of new blood vessel formation, in 4 to 6 weeks. Old age spots typically begin to fade in 4 to 8 weeks of treatment. Fine lines and wrinkles diminish after about 4 months of treatment. Some of these changes may persist for up to 4 years. Long-term benefits generally require continued long-term treatment.8

In addition, Dr. Kligman found that pairing tretinoin with alpha hydroxy acids seemed to boost its effectiveness. His research indicated that the two products, applied at different times of the day, produced greater benefits than the use of tretinoin alone at night, while not increasing the side effects. The two products used together appeared to effectively target the early signs of skin aging such as fine lines and uneven pigmentation.3

Generally priced in the $100 range for a 45-gram tube, tretinoin is not an inexpensive treatment. Most health insurance does not cover tretinoin for people over the age of thirty-five when the effectiveness of tretinoin for the treatment of acne generally declines and people of a certain age begin to request it for its “anti-wrinkle” benefits.

Many of the histological markers of photodamaged skin have been identified. The major histological changes that occur in skin as a result of tretinoin treatment appear to be specific and directed at restoring skin structure and function. The most rapid clinical improvement is usually seen in the first six to twelve months.2 Most plastic surgeons agree that treatment needs to be continuous for the best results to be achieved and maintained.

References


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Stem Cells and Cloning: What Does it Mean to Be Human?

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New technologies have given us never before seen powers of intervention in human life and the environment, powers so immense that regulation and supervision are needed, in both research and in the utilization of research results. From the beginning of the use of new technologies, an important point of discussion has been the concept of the quality of life, focusing on the problems that modern medicine and biotechnology must solve in order to grant the highest health standards to the largest possible number of people. Some of the main issues concerning the boundaries of life are: the status of an embryo, human cloning, genetic trials on humans, artificial fertilization, contraception, sterilization, abortion, euthanasia, organ transplantation, and suicide. There is a strong difference of opinion between those who hold various bioethical perspectives. On the one hand, there are those claiming individual autonomy as supreme, and, on the other hand, those stressing the existence of changeless and universal laws in human nature, laws that must be recognized and observed in order to promote both individual and common good. This review article explores the debate on stem cell research and cloning, the positive and negative consequences of the research, and the ethical issues presented by the research.

Embryonic stem cells, found within embryos prior to implantation, have the potential to create tissues that can be given to patients whose own tissues are missing or diseased. The possibility of using embryonic stem cells for cell-replacement therapy in diseases like diabetes mellitus is under investigation. Stem cells from a number of different lineages are being used for research to see how these therapies can be accomplished.

There has been concern by some on how stem cells are obtained for such scientific research. Since deriving stem cells from early embryos in the blastocyst stage (about 14 days old) implies that the embryos are destroyed, the use of human embryonic stem cells has created fierce debate. Generically, stem cells are immature cells that develop into the mature, differentiated cells to make up the adult body. Fertilized eggs are the ultimate totipotent cells capable of producing all cell types. It can be argued that animal development is a progressive loss of totipotency (cells that can give rise to a new individual if provided with appropriate maternal support), followed by pluripotency (cells capable of giving rise to all tissues of the body plus many of the cells that support pregnancy but are unable to produce a new individual on their own), and finally differentiation into specific cell types. Embryonic stem cells are pluripotent whereas trophoblast stem cells can differentiate only into the trophoblast lineage. It is now possible to coax blood stem cells and neural stem cells to become some other types of mature cells. A stem cell continues to grow and proliferate, maintaining a pool of cells for possible use, and given the correct signals, a stem cell can differentiate into a particular specialized cell type.

Recent studies suggest that tissue-specific stem cells can differentiate into cell lineages other than the tissue of origin, and mesenchymal stem cells derived from adult marrow have been shown to proliferate extensively without loss of differentiation potential. Thus, they may be an ideal cell source for therapy of inherited or degenerative diseases. It has also been shown that a substantial number of organ fibroblasts appear through a novel reversal in the direction of epithelial cell fate, highlighting the potential plasticity (ability of an adult stem cell from one tissue to generate the specialized cell type or types of another tissue) of differentiated cells in adult tissues under pathologic conditions.