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Stem cell activation for smoother, more even skin

The skin forms a barrier that protects us against dehydration and external threats. This barrier function is provided mainly by the outer skin layer, called the epidermis. This layer is constantly renewed; cells that are shed from the outer layer, the *stratum corneum*, are replaced by newly formed cells from the inner layer of the epidermis. This constant renewal is important for the quality of the barrier and keeps the skin smooth and even. The epidermal turnover time is about one month. But between our thirties and eighties the turnover rate reduces by 30% to 50% leading to a much longer turnover time. The consequence of the slowdown of the renewal in elderly people is a dry, rough, uneven and dull skin.

Symphytum officinale.

Tissue regeneration depends on adult stem cells

Stem cells possess three key properties: they are unspecialised, they can renew themselves over long periods, and they can develop into cells with specific functions. They are broadly classified into two types, embryonic stem cells and adult stem cells. Embryonic stem cells are pluripotent, meaning that they can develop into all cell types of the body, and are thus capable of forming an entire organism. In contrast adult stem cells in general are multi-potent, only able to develop into the different cell types of the tissue in which they are found (a process known as differentiation). Adult stem cells are found in virtually all tissues. Using a remarkable process known as asymmetrical division, they are able to both maintain the pool of adult stem cells throughout an organism's entire lifespan, and to provide the continual supply of new cells essential for repair and regeneration. Without an effective pool of adult stem cells able to proliferate as required, the continual loss of fully differentiated cells cannot be replenished, and the tissue soon loses the ability to function.

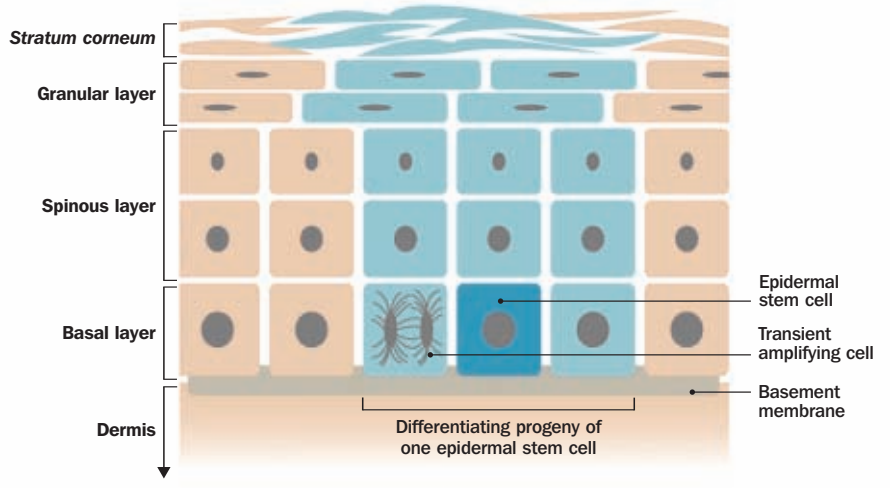

Figure 1: *Epidermal stem cells located in the basal layer.*

Decline in stem cell activity responsible for reduced renewal of the epidermis

Responsible for the constant renewal are epidermal stem cells that are dispersed in the inner layer of the epidermis (Fig. 1). Only these cells have the potential to generate new cells for tissue renewal. These cells represent approximately 2% to 7% of the total cells in the epidermis. Undifferentiated cells in the epidermis can be identified *in vivo* via label-retention studies enabling detection of slow-cycling cells, and by the expression of specific marker proteins such as α6-integrin and CD34. Following asymmetrical division, epidermal stem cells produce more rapidly dividing transient amplifying cells, which after a limited number of divisions enter terminal differentiation. As the cells differentiate, they migrate up through the epidermis, finally forming the uppermost *stratum corneum*. At this point, the cells have ceased proliferation, lost their nuclei, and serve only as a physical barrier.

With age the turnover of the epidermis is reduced, making it thinner, more fragile, and more likely to suffer from impaired wound healing. It has been found that epidermal cells isolated from older donors have a lower stem cell function than epidermal cells originating from younger donors. Also the rate of propagation of these cells is known to be reduced in elderly people (Fig. 2). This is the principal reason for the reduced turnover rate and thus for the slowdown of the epidermis renewal with advancing age.

Comfrey stem cells to activate renewal of the epidermis

PhytoCellTec Symphytum [INCI: Symphytum Officinale Root Cell Extract, Isomalt, Lecithin, Sodium Benzoate, Aqua] was found to activate the propagation rate of our epidermal stem cells. It thus restores the renewal potential of aged skin. PhytoCellTec Symphytum is an extract of comfrey stem cells. Comfrey is a perennial shrub with purple or pink flowers, native to Europe, growing in damp, grassy places.

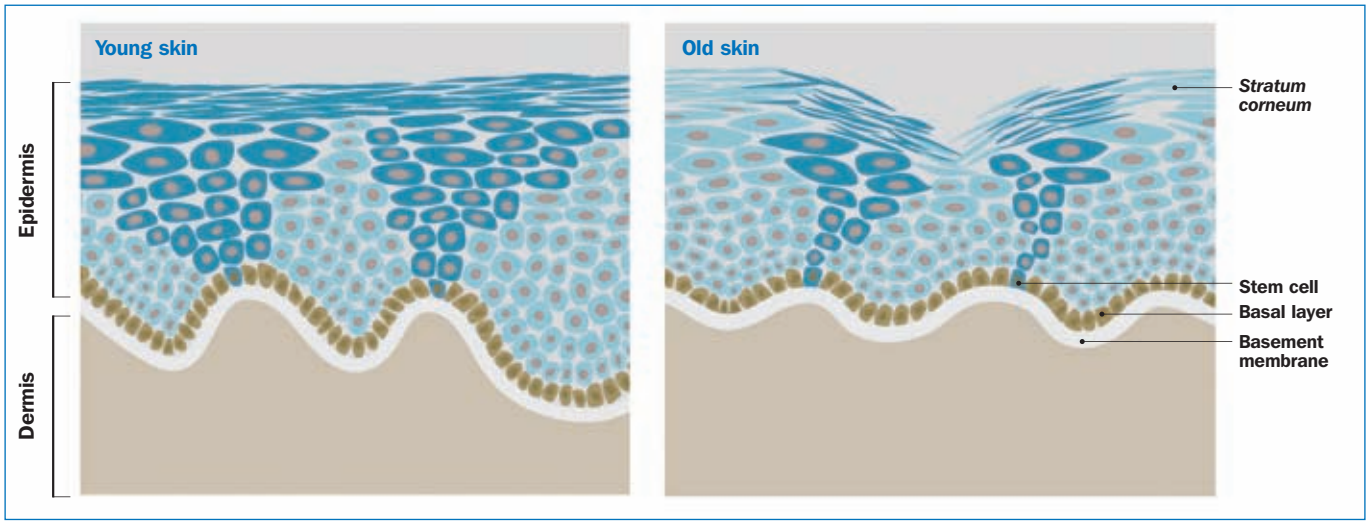

Figure 2: *Age-related turnover.*

Comfrey is used as herbal medicine, mainly for skin treatments. Comfrey ointments are applied for wound healing and the treatment of bone fractures. Plants also have stem cells. Two populations of stem cells, one comprising the shoot apical meristem and the other the root apical meristem, create the plant body. The plant tissue culture technique is based on propagation of plant stem cells either to produce a whole plant, only tissue or just single cells in culture to harvest plant metabolites. This practice allows the production of plant material under sterile and standardised conditions independent of season and other environmental restraints. Plant tissue cultures can be initiated from nearly all plant tissues. The tissue material which is obtained from the plant to culture is called an explant. As a kind of wound reaction, new cells are formed on the cut surfaces of the explant. The cells slowly divide to form a lump of cells which is called callus. These cells have de-differentiated into cells that lack the distinctive features of normal plant cells. Callus cells are stem cells comparable to those in the meristem regions. For high yield production, callus cells can be cultured after homogenisation of the suspended cells in a liquid culture. Comfrey roots were used to obtain tissue explants in order to initiate a plant stem cell culture. An extract of these comfrey stem cells was tested in a series of studies for anti-ageing efficacy in skin.

Efficacy studies with the comfrey stem cell extract

For cell culture assays with human epidermal stem cells, a new technique known as progenitor cell targeting (developed by CELLnTEC Advanced Cell Systems) was used to establish enriched cultures of progenitor/stem cells direct from a skin sample. This technique uses specialised culture media to specifically mimic the environment of the stem cell niche. FACS analysis has demonstrated that this method rapidly selects and enriches the valuable undifferentiated cells found in primary keratinocyte cultures. For example the percentage of cells expressing the markers CD34 and α6-integrin has been found to increase from 6% to 68% during the first 3 passages of culture (Fig. 3). Using these enriched cultures, the positive effect of the comfrey cell extract on the propagation rate of epidermal stem cells was discovered. To mimic the tissue environment of elderly people, a cell culture medium was developed that contained the essential elements but was devoid of protecting and stimulating compounds. The proliferation of isolated epidermal stem cells cultured in this ageing medium was clearly reduced compared to a normal medium. But epidermal stem cells cultured in the ageing medium supplemented with low amounts of the comfrey cell extract proliferated much more than in the control culture without comfrey cell extract. The comfrey cell extract was also found to improve morphology and hyaluronic acid content in epidermis models formed in the ageing medium.

Next, the comfrey cell extract was formulated into a vehicle cream and was tested in a clinical trial with 20 women, aged between 40 and 60. After 4 weeks' application, a significant increase in the skin renewal rate was found. Concomitant, skin smoothness analysis by PRIMOS showed a 12% improvement.

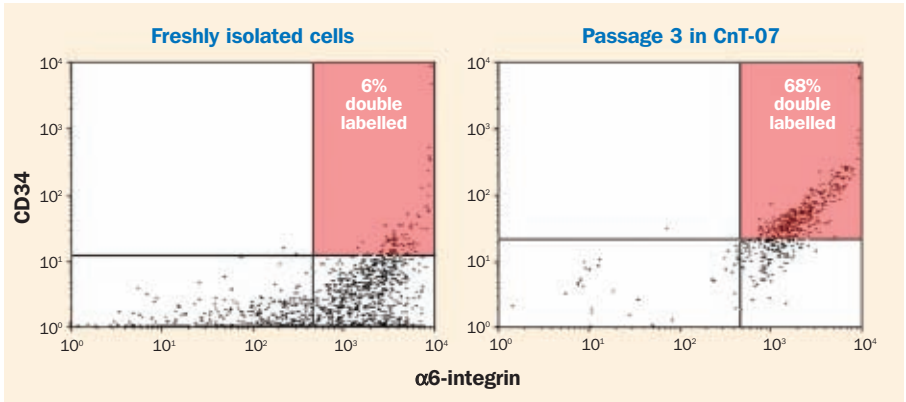

Figure 3: *CD34 and α6-integrin expression.*

Conclusion

As we get older, the skin renewal slows down leading to an uneven surface and the formation of scales. This has a negative influence on skin complexion and makes the skin look dull and grey. Instead of using irritating peeling procedures, Mibelle Biochemistry Group proposes PhytoCellTec Symphytum to get down to the root of the trouble. Epidermal renewal starts at stem cells dispersed in the inner layer. The proliferation capacity of these cells and of their next progeny defines the epidermal turnover rate. It is known that their proliferation is reduced in elderly skin.

PhytoCellTec Symphytum stimulates the proliferation of these cells compensating for the usual deterioration during ageing. It leads to an improved epidermal turnover rate and finally to a smoother skin and to a much better skin complexion. PC