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# Rejuvenation through epigenetic science

Franziska Wandrey\*, Daniel Schmid

\*Corresponding author

Mibelle Biochemistry, Switzerland

May 2016

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## Abstract

*The mystery of the queen bee's special diet – royal jelly – has been deciphered: the active component royalactin is the one essential factor that drives all the changes needed to make a queen bee. This protein activates the epidermal growth factor signalling pathway, which is a crucial regulator of the ageing process. Mibelle Biochemistry presents RoyalEpigen P5: a five amino acid peptide designed to use the power of royalactin to reactivate the youth trigger in our skin.*

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## One genome – Two fates

The honeybee (*Apis mellifera*) forms two female castes: the queen and the worker. While the queen bee is large in size and specialised in reproduction, the workers are small and engaged in activities for maintaining the colony. The queen bee lives far longer than any other bee in the hive. She is more resilient with respect to extrinsic environmental stress factors, such as thermal stress and has a slower intrinsic ageing process in comparison to worker bees. Despite their vastly different appearance, physiology and behaviour, queen and worker bees share the same genome. They differ only in which genes are activated and hence which proteins are produced to serve specific functions. In fact, young queen larvae produce higher levels of proteins involved in amino acid metabolism, energy production and repair, a prerequisite for tissue growth. How does it work? Honeybees modify their genetic code by consuming a special diet called royal jelly (RJ). This peculiar juice leaves chemical “markers” on the DNA, which modify gene expression without actually changing the genetic code – a process referred to as “epigenetic” modification (“on top of the genome”). Thus, RJ is the epigenetic trigger that determines a honeybee larva's fate.

## Royalactin – the “queenmaker” in Royal Jelly

The mechanism of action and active ingredient of RJ, however, was a mystery until 2011, when a Japanese scientist discovered the “queenmaker” protein royalactin. This 57 kDa protein is the one crucial factor that drives all the changes needed to make a queen bee. Interestingly, the effects of royalactin are not just limited to bees. Scientific studies have revealed a kind of “cell doping” effect in other insects. For example, royalactin increases longevity in fruit flies. In mammals, on the other hand,

royalactin was reported to enhance proliferation in rat liver cells. All of these effects are due to the putative interaction of royalactin with the epidermal growth factor (EGF) receptor. Activation of the EGF signalling pathway not only triggers the development of a regular honey bee larva into a queen, but it is also promotes tissue regeneration and delaying signs of senescence in human skin cells.

Interestingly, only fresh RJ is fully potent. This is due to the quick degradation of royalactin after a short time of storage. Mibelle Biochemistry developed the pentapeptide TRSEL, to mimic an active site of royalactin. Encapsulation of the peptide into a nano-structured lipid matrix ensures its delivery to the target skin layer without losing any activity.

## RoyalEpigen P5 triggers skin cell's regenerative capacity

The regenerative potential of a cosmetic active can be tested in an *in vitro* wound healing assay. In short, the basic step involves creating an “artificial wound” in a cell monolayer, capturing images of the preparation at the beginning and at regular intervals during cell migration, which eventually closes the wound. RoyalEpigen P5 shows the remarkable capacity to accelerate proliferation and migration of keratinocytes to efficiently close the lesion (Figure 1). The obtained images indicate a potent regenerative effect of the peptide, indeed very similar to the reference compound EGF.

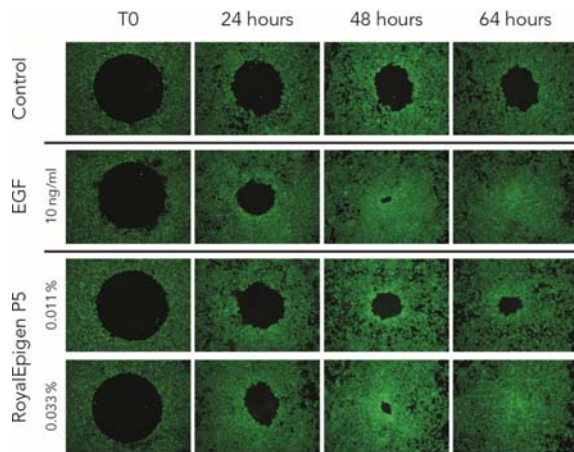


Figure 1: Wound healing assay. The peptide stimulates NHEK proliferation/migration. The effect is similar to the reference EGF.

### RoyalEpigen P5 improves protein quality

By activating EGF signalling, royalactin clearly targets a crucial regulator of the ageing process. Scientific studies have shown that activation of the EGF pathway leads to the stimulation of the Skp-1 like adaptor, a key-limiting factor in the ubiquitin-proteasome system (UPS). The role of UPS is to recycle damaged proteins and to maintain high protein quality. A highly active UPS was found in skin cells from centenarians. A gene expression study performed on human keratinocytes revealed that RoyalEpigen P5 stimulates the synthesis of SKP1 in keratinocytes by 197% (control 100%). Additionally, a proteomic study performed on senescent keratinocytes confirmed that the peptide attenuates the age-dependent reduction of proteasome subunits, ribosomal components and chaperones, consequently promoting protein turnover and protein repair.

### Clinical study

Restoring a healthy population of various proteins in aged keratinocytes correlates with visible skin benefits as demonstrated during *in vivo* studies. Twenty volunteers (average age 49) with inhomogeneous skin tone participated in a placebo-controlled study. A cream containing 2% of RoyalEpigen P5 was applied twice a

day for 28 days to the inner side of the forearm and the face. The renewal time of the stratum corneum decreased by almost 3 days resulting in a much smoother skin surface (+16%). An effect was observed in 100% of the volunteers. The peptide was found to significantly improve skin tone homogeneity in 80% of the volunteers (Figure 2). RoyalEpigen P5 preserved the biomechanical properties of the skin; skin firmness was improved by 14%.

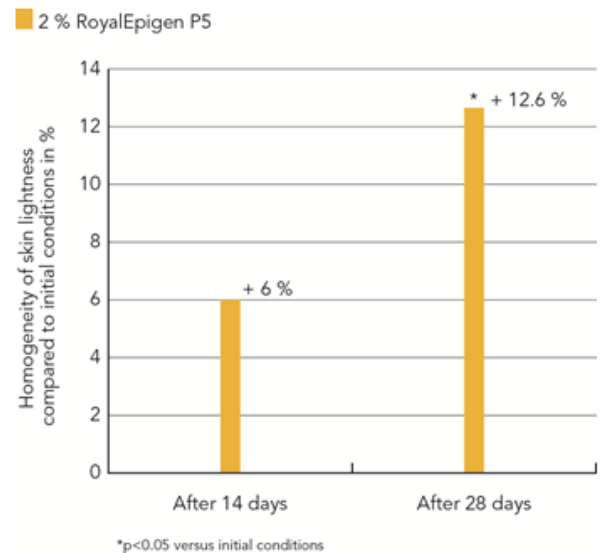


Figure 2: Improvement of skin homogeneity after treatment with 2% RoyalEpigen P5.

### Conclusion

The outside world can have a direct effect on cellular DNA. RoyalEpigen P5 is based on the queen maker protein royalactin, the magic factor that converts a regular honeybee larva into a queen. The five amino acid peptide accelerates keratinocyte proliferation for a strong regenerative effect. RoyalEpigen P5 promotes SKP1 upregulation in aged skin cells resulting in rejuvenation of specific protein populations. This new active ingredient keeps the skin supple and gives it a smoother texture and more even appearance.

Bolimattstrasse 1, 5033 Buchs / Switzerland  
 Phone: +41 62 836 17 31 Fax: +41 62 836 14 05  
 info@mibellebiochemistry.com, www.mibellebiochemistry.com

