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Complicated Hyaluronan Patterns in Skin: Enlightenment by UVB?

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Hyaluronan has a complex metabolism with rapid turnover in skin, with wide differences occurring in dermal and epidermal compartments. Analyses of acute UVB irradiation of skin, as documented in cultured human fibroblast and immortalized keratinocyte cell culture media, confirm that no simple patterns are present. A systematic approach has been initiated in the studies by Averbek *et al.*

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UVB represents only 0.5% of the sunlight reaching the Earth's surface but is far more skin-penetrating than any other components of sunlight. It also accounts for much of the acute and chronic sun-related damage to skin. Hyaluronan (HA) is a non-sulphated, straight-chain glycosaminoglycan polymer of the extracellular matrix. Half of total-body HA is located within skin, where it is responsible for skin hydration. It occurs at much-increased levels in response to injury and repair. Its turnover rate is very rapid, with a 1/2 life of 2–5 minutes in the circulation (Fraser *et al.*, 1981) and 1–2 days in the epidermis (Reed *et al.*, 1988). The turnover rate in the dermis, however, where most skin HA occurs, is not clear. Nor is dermal metabolism of this important polymer understood. HA metabolism in skin is even more complex than formerly assumed.

Histological and biochemical analyses of HA metabolism following chronic UVB exposure in mice have been contradictory. Some report

an increase, whereas others report no change. Vastly different mechanisms for regulation of HA deposition occur within the two skin compartments, with separate profiles of growth factors and cytokines affecting the enzymes that modulate deposition.

Half of total-body HA is located within skin, where it is responsible for skin hydration.

To initiate systematic examination of HA metabolism, a study of short-term UVB irradiation was undertaken. Cultured human dermal fibroblasts and epidermal keratinocytes were used as paradigms of their respective compartments. A differential response to short irradiation was observed, involving complex temporal and spatial patterns. Net HA deposition is the result of an equilibrium between HA synthesis by the three HA synthases and catabolism

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by the several hyaluronidase (HYAL) enzymes. HYAL1 and HYAL2 account for most of the catabolism in somatic tissues, including skin (Stern, 2004).

HYAL2, an enzyme that is partially cell membrane-associated and partially soluble, depending on the tissue source, makes an initial cut in the huge 10^5 - to 10^7 -dalton extracellular polymer to generate oligomers of 50 to 100 disaccharides. These are then taken up and delivered to early endosomes and lysosomes for further degradation by HYAL1 and the acid-active exoglycosidases, and catabolized down to tetrasaccharides and single sugars. The point at which external HA degradation ceases and internal catabolism is initiated is not at all clear.

As in most biological systems, size is critical. Recent observations indicate that the HA polymer has a myriad of biological functions dependent on molecular size. The extracellular large HA polymer is anti-inflammatory and antiangiogenic and is a marker for intact healthy tissue. The HA fragments, which are usually signals for tissue injury, constitute an information-rich system (Stern *et al.*, 2006). The first scission reaction catalyzed by HYAL2 generates fragments that are highly inflammatory, are highly angiogenic (Noble, 2002), and can ultimately initiate a fibrotic response. Such HA fragments were recently invoked as mechanisms that can contribute to scleroderma (Neudecker *et al.*, 2004) and the scleromyxedema-like lesions occasionally seen in patients in renal failure (Neudecker *et al.*, 2005).

To add to the complexity, HA is itself damaged by UVB, with degradation occurring also as a result of free oxygen radicals (reactive oxygen species) and Maillard products.

As Averbeck *et al.* (2007, this issue) now demonstrate, 3 hours after short

UVB exposures, HA levels decrease in both keratinocyte and fibroblast culture media. After 24 hours, however, HA levels are increased in keratinocyte culture media, but decreased in fibroblast culture media. This is supported by mRNA analyses of the respective enzymes. HA synthase mRNA levels are increased in both types of cell cultures 24 hours after exposure, whereas HYAL levels are elevated only in fibroblast cultures. Surprisingly, analysis of dermal microdialysis fluid obtained *in vivo* in the human did not contain inflammatory-sized HA fragments, but rather the products of further HA degradation.

HA supports and facilitates tumor progression. Stromal HA is a prognostic indicator for poor outcome in a number of malignancies (Boregowda *et al.*, 2006), including malignant melanomas. Components of the molecular basis for HA promotion of malignant melanomas are beginning to be described (Ahrens *et al.*, 2001), reflecting the resourcefulness and resilience of cancers in commandeering normal injury response pathways for their own advantage.

Slightly elevated HA levels in the epidermis after UVB exposure may occur body-wide, in a type of sympathetic response. This may explain the curious phenomenon of malignant melanomas occurring in non-sun-exposed areas after extensive UVB exposure. The other proviso for the dermatology community to consider is the silent concern that many skin fillers are HA-based. Whether such locally injected HA can have long-term effects, by supporting the occasional transformed cell, remains to be seen.

HA has a repeating disaccharide structure that is exceedingly simple. However, it obviously has an enormous repertoire of functions. The complex differences in HA metabolism between the two compartments

of skin add to its profound nature. HA is also recognized now as critical for supporting the stem-cell niche, including that of the bulge of the hair follicle. It has come a long way since its initial description in 1934, including having its name changed, from hyaluronic acid to hyaluronan. Perhaps it should be renamed once again to reflect its complexity. "Highly ionic acid" perhaps?

CONFLICT OF INTEREST

The author states no conflict of interest.

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