

Advances in molecular biology continue to widen our understanding of the function of DNA and proteins. The study of polysaccharides as the third major class of macromolecules in the body only recently gained momentum. Polysaccharides are amongst the most diverse biological compounds, yet their role as information carriers does not often appear to receive the degree of attention it deserves. This communication points out the potential significance of hyaluronan (HA) as an information system and proposes a significant and multifaceted role of this versatile molecular system as an early tissue damage signal.

It has become increasingly evident that HA plays a much more dynamic role than just a lubricating, fluid- and salt-binding, and filtering component of the extracellular matrix (ECM). With a ~12 hour half life in skin and joints, it has a surprisingly high turnover rate – about 30% of total body HA is removed and replaced each day. Lymph nodes are the main sites of HA degradation (~90%), resulting in continuous release of low molecular weight fragments (LMWHA) [1]. Recently, we have shown that HA can be used as a lymph propulsion marker in humans under various physiological conditions [2,3].

Despite its structural simplicity, HA specifically interacts with binding proteins and proteoglycans. It is involved in a wide array of phenomena like morphogenesis, embryonic development, tissue stability, cell proliferation, remodelling, migration, differentiation, angiogenesis, or wound healing. Inflammatory conditions increase HA levels in tissues and body fluids, as with lung fibrosis, rheumatoid arthritis, myocardial infarction and transplant rejection, as well as invasive processes [4]. LMWHA trigger

cytokine and adhesion molecule production. They also induce nitric oxide synthase in macrophages, resulting in connective tissue destruction and further macrophage recruitment. HA, particularly LMW, rises with inflammatory disease and induces prostanoic acid production via increased COX-2 expression [5]. Even arthropathies are associated with a reduction in HA-chain length.

After tissue injury, LMWHA rapidly accumulates in affected interstitial spaces [6]. Importantly, this occurs prior to the arrival of activated immunocytes and collagen deposition. A variety of mechanisms seem to cause LMWHA accumulation – depolymerisation by granulocyte-derived reactive oxygen species (ROS) as well as ultraviolet radiation, tumour genesis, enzymatic cleavage, mechanical stress, or *de novo* synthesis by hyaluronan synthases such as HAS3, the most active of the hyaluronan synthases that produces short-chain HA [7]. Some pathogenic bacteria use HA lyases as a virulence factor for facilitating invasion of tissues and oligosaccharides derived by this enzymatic action might act as first proinflammatory mediator.

These observations suggest LMWHA functions as an early signal of challenged ECM status, contrary to the preponderance of high molecular weight HA that would code undisturbed homeostasis [8].

HA size seems to be crucial for the mode of cellular interaction depending on cell type – only fragmented <250 kDa HA induces inflammatory gene expression in macrophages in contrast to the native HA from which it was prepared. High-molecular-weight HA even suppresses endothelial cell growth at high concentra-

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tions, thereby being anti-angiogenic, whereas LMWHA stimulates cell growth, induces angiogenesis and endothelial cell migration [9].

HA interacts with specific cell-associated receptors, collectively referred to as hyaladherins such as CD44 or RHAMM (receptor for hyaluronan-mediated motility). CD44-positive lymphocytes interact with endothelial HA, move to sites of inflammation and contribute to various activation processes like T-cell activation and lymphopoiesis. The relatively weak binding of CD44 to HA may facilitate transient adhesion, triggering intracellular cascades as required for proliferation or migration [10]. Similarly, integrin-associated differentiation of human thymocytes depends on HA binding to RHAMM and elicits cellular signal transduction and locomotion. These information pathways can also be employed by bacteria (e. g., group A streptococci) that have capsular HMWHA, protecting them from phagocytic attack.

A mutual boost also exists because gene expression of HAS3 is markedly enhanced by inflammatory cytokines such as IL-1 β and TNF- α [11]. This suggests a positive feedback loop where different proinflammatory stimuli trigger unspecific degradation of HA. On the other hand, overexpression of HAS3 even enhances tumour-cell growth, extracellular matrix deposition, and angiogenesis. In contrast, HAS2 produces significantly more HMWHA and is markedly suppressed by hydrocortisone which does not influence HAS2 activity [12].

Interestingly, a similar mechanism can be observed in plants. Chitin is a major component of the cell walls of various fungi and fragments of chitin stimulate defence responses in many plants. The fragments induce biosynthesis of phytoalexins, newly synthesised antimicrobial compounds of low molecular weight, and stimulate various early cellular responses such as membrane depolarisation, a transient increase in ion efflux, alkalisation of the medium, generation of ROS as well as the expression of several unique early responsive genes [13].

In conclusion, stress-induced fragmentation of HA seems an important mechanism to activate corresponding immunological pathways. We suppose that sorting of damage-coding signals based upon molecular size constitutes an important information pathway [9,14,15]. From an evolutionary point of view, this would represent an elegant way of signal transport for tissue homeostasis and protection.

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