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Opinion
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Do Normal Human Epidermal Keratinocytes Require a Priming Step to Activate the NLRP3 Inflammasomes to Exogenous Threats?

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Opinion

In recent work examining the expression of inflammasome-induced release of active Caspase-1 on Normal Human Epidermal Keratinocytes (NHEK), it was noted that two exogenous threats, UVB radiation and ATP were effective at activating the NLRP inflammasomes and inducing the release of significant quantities of active Caspase-1 [1]. It is generally thought that activation of the NLRP inflammasomes is a two-step process requiring: 1) activation of the NLRP inflammasome by signaling from the Toll-Like Receptors (TLR), and 2) creation of the inflammasome proteins after transcription via NF-ƙβ nuclear signaling, assembly of the inflammasome complex and subsequent activation of Caspase-1 upon binding to the ASC binding domain of the inflammasome [2]. Active Caspase-1 then begins to cleave inert cytokines such as IL-1β and IL-18 and causes the activation of gasdermin D, a transmembrane pore-forming protein, that initiates a form of cell death called pyroptosis that commences the downstream processes of inflammation. In the recent work examining the impact of various exogenous threats on Normal Human Epidermal Keratinocytes, employing the Promega® Caspase Glo®1 Assay, the original data indicated that after the cells were exposed to both UVB radiation and ATP, within the first 3 hours after exposure there was no appreciable increase in the expression of active Caspase-1 [1].

However, after 20 hours, the two exogenous influencers caused a statistically significant, dose-dependent increase in active Caspase-1 release indicating that somewhere between 3 and 20 hours, the exogenously treated cells began to express active Caspase-1 without an apparent initial priming step. It appears that the NHEKs were self-priming the release of active Caspase-1 without the initial anticipated priming requirement of messaging from the Toll-Like Receptors. Recently, Gritsenko et al., published work suggesting that human monocytes could be self-primed to express active Caspase-1 when exposed to the LPS nigericin [3]. This work was one of the first papers to suggest that human cells might be able to form canonical inflammasomes without the need for a priming step. Such findings are fundamentally important as they suggest these critical defense mechanisms may develop through yet not completely understood processes that do not require an initial priming step through the Toll-Like Receptors to initiate the innate immune inflammation response. It suggests, instead, that the inflammasomes themselves may be the primary initiators of the cellular release of active Caspase-1 under certain circumstances. Certainly, when considering the role of various cells that face external threats such as epidermal keratinocytes or lung epithelial cells, which are now known to respond to the SARS-CoV-2 virus by inflammasome activation, whether the cells need a priming step or not is important to understanding not only the role of inflammation in the body, but more importantly, how various cell lines may operate differently depending on their needs [4].

It may be that cells that are in direct contact with exogenous threats like epidermal keratinocytes, and eye, throat and lung epithelial cells may respond more directly to threats by direct induction of the innate immune response while other more downstream immune cells may require some type of priming step to activate. This makes some sense as the body would not want to have its adaptive immune response "turned on" all the time without some element of feedback control like a priming

step. One the other hand, cells prone to contact with external threats like energy (UV), chemicals (ozone or PM2.5 particles), or microbial or viral threats, all of which have been shown to initiate inflammasome activation in NHEKs, might need to respond more directly to the threats. All of this may sound a little like how many angles can dance on the head of a pin, but it may also be critical in life threatening diseases such as COVID where treatments are being developed that can help suppress the NLRP inflammasome response that can lead to sepsis while not completely shutting down the inflammation response needed to clear the viral threat. In skin, it is known that most cells associated with the epidermis and dermis can express NLRP inflammasome proteins and they can likely act as initiators of the innate immune response. When discussing topical treatments that may impact inflammasome induced effects, particularly the processes that can lead to prolong inflammation and the aging process called inflammaging, better understanding of the mechanisms by which the cells respond can make topical therapeutics and cosmetics more effective treatments.

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