February 19, 2008

Of viruses, tolls, TREMS and interferons

RIKEN researchers expand our understanding of how the immune system produces specific antiviral proteins in response to viral infections.

The human body's defense against viruses is complex and much remains poorly understood. More light has now been shed on this enigmatic field by researchers from RIKEN's Research Center for Allergy and Immunology that they have identified a new cell surface protein critical to the antiviral response. The RIKEN team has characterized how this new player works in concert with a network of other proteins to quickly boost the production of extremely potent antiviral agents called interferons (IFNs).

The IFNs comprise a variable group of proteins that are generally only produced upon immune system activation. IFNs are part of the immune system's non-specific response and therefore represent the earliest defenses mounted against any invading viral pathogens, long before more specific immune reactions can be marshaled. The main types of human IFNs are classified as either Type 1 or Type 2 IFNs; IFN-a and IFN-b the most common Type 1 IFNs, are produced by virus-infected cells, and are very effective at protecting other cells from infection by reducing viral multiplication.

Although IFNs are often defined by their antiviral activities, many of these proteins are multifunctional. Indeed, the effects of IFNs extend beyond immunomodulatory consequences to encompass a wider spectrum of hormone-like activities and possibly even anti-inflammatory mediation. Among the most prolific producers of IFNs are dendritic cells (DCs), which are a specialized type of immune system cell.

Since DCs are the key orchestrators of an activated, specifically 'customized' and hence delayed immune response, it is somewhat paradoxical that they also produce IFNs, the non-specific, generic elements of early responses. Of the distinct DC subpopulations that have been identified, plasmacytoid DCs (PDCs) typically produce the highest Type 1 IFN quantities when exposed to viruses.

PDCs are known to respond to external stimuli through 'toll-like receptors' (TLRs), cell surface proteins that are one of the critical elements of the PDC-IFN activation pathway. When a specific molecule that can stimulate an immune response docks in a TLR, it

triggers a signaling cascade of secondary events, which include signals mediated by other proteins called type 1 IFN-a/b receptors (IFNARs). Because TLR activity alone cannot explain how these events collectively generate optimal IFN production, the RIKEN researchers focused on searching for new players in this IFN activation pathway.

The researchers used 'proteomics' - studying proteins on a large scale - to identify a new cell surface receptor they designated 'PDC-TREM' that allows PDCs to produce amplified IFN levels. By examining spleen cells from normal and genetically modified mice strains, the authors determined that PDC-TREM is unique among PDC-specific molecules in that its surface expression is inducible - requiring both TLR- and IFNAR-signaling - and it cannot be detected on unstimulated PDCs.

The scientists also elaborated roles for several other proteins - PlxnA1, Sema6D, DAP12 - that either form active complexes with PDC-TREM or induce its expression. The authors studied changes during IFN production in the concentrations of these new elements of the PDC-IFN activation pathway and were able to delineate how this PDC-TREM-mediated signaling cascade drives appropriate, measured responses between various effector proteins and their downstream targets, although much remains to be elucidated. Crucially, the RIKEN's group illustrated that interfering with or disrupting PDC-TREM expression and/or activity severely inhibited the signaling process and IFN production. Their work has clearly demonstrated that PDC-TREM is intimately involved with the augmented IFN production that characterizes PDCs.

Since viruses often evolve sophisticated mechanisms to overcome IFN-mediated reactions, the RIKEN team's findings should help us to understand enough about IFN biology to hopefully keep viral scourges at bay.

Original work:

Watarai, H., Sekine, E., Inoue, S., Nakagawa, R., Kaisho, T., Taniguchi, M.
PDC-TREM, a plasmacytoid dendritic cell-specific receptor, is responsible for augmented production of type I interferon, *PNAS*, published online on Feb. 18, 2008

For more information, please contact:

RIKEN Public Relations Office
Email: koho@riken.jp