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Editorial

ICE Heats Up

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Not all caspases are as focused on apoptosis as some of us are. In fact, the first identified caspase (before there *were* 'caspases') was interleukin-1 converting enzyme, or ICE, now called caspase-1. In this issue of CDD, Druilhe *et al*[1] describe proteins that bind to and regulate the activation of caspase-1. Although caspase-1 can process and activate caspase-3 and trigger apoptosis in some cases, its major role appears to be in cytokine processing. In particular, caspase-1 cleaves pro-interleukin 1b and pro-interleukin-18 (another member of the IL-1 family) to their mature, secreted forms. Mice lacking caspase-1 are developmentally normal (unlike knockouts of caspases 3, 8, or 9) but cannot secrete IL-1β. As a consequence these animals are resistant to endotoxic shock (which is mediated in part by IL-1), and this may account for their relative resistance to some forms of ischemic injury.

While a great deal has been learned about the mechanisms of caspase activation during apoptosis, the activation of caspase-1 has been less well understood. Caspase-1 contains a large prodomain with a CARD (caspase recruitment domain), and it is probably through oligomerization that the caspase auto-activates.[2,3] The best candidate for an adapter molecule responsible for the oligomerization and activation of caspase-1 is a molecule alternatively called RIP2, CARDIAK, or RICK.[4–6] Caspase-1 binds to RIP2/CARDIAK via a CARD-CARD interaction.[5]

Druilhe *et al*[1] describe and analyze two proteins that interfere with the activation of caspase-1. One of these, Pseudo-ICE (which has not been described previously), binds to the CARD domains of caspase-1 and of RIP2/CARDIAK and prevents interactions that activation caspase-1. In this it is more active than the second protein, ICEBERG, which was described previously and its inhibitory activity analyzed. ICEBERG binds to caspase-1 via a CARD-CARD interaction, and this presumably prevents oligomerization and activation.[7]

Interestingly, both Pseudo-ICE and ICEBERG closely resemble the prodomain of caspase-1. Pseudo-ICE shares 92% identity with this region, and while ICEBERG is a bit more divergent, its structure is that of a CARD.[7] Both of these map to the same chromosome region (11q22 in human) that harbors caspase-1, as well as two caspases of unknown function, caspases-4 and -5. This remarkable similarity between a caspase and its regulators is reminiscent of the relationship between caspase-8 and its regulators, c-FLIP.[8,9] Two isoforms of c-FLIP are known; one of these, c-FLIPs, resembles the prodomain of caspase-8 and is therefore analogous to Pseudo-ICE and ICEBERG. The long form of c-FLIP, however, shows extensive homology with caspase-8 for its entire length, but lacks an active cysteine where the catalytic site of a protease would be. Nevertheless, the theme is the same – one way to block the activation of a caspase is to mimic that caspase.

The binding of Pseudo-ICE to both RIP2/CARDIAK and caspase-1 presents an interesting dilemma. The CARDS of two interacting molecules are complementary, allowing specific electrostatic and/or hydrophobic interactions. Therefore the CARD of Pseudo-ICE should interact with caspase-1 CARD *or* the CARD of RIP2/CARDIAK (since these interact with each other). However, different CARD domains utilize different surfaces for interaction, and it is therefore formally possible that Pseudo-ICE binds to both partners using different sides of this domain. Mutational analysis should effectively test this idea.

Interleukin-1 is an inflammatory cytokine that is produced by monocytes, macrophages, and other cell types in response to bacteria and other potential invaders. Both Pseudo-ICE and ICEBERG inhibit this response, as do peptide inhibitors of caspase-1. But how does the presence of bacteria trigger the activation of caspase-1 for the processing and secretion of pro-IL-1? Bacterial lipoproteins and bacterial DNA (CpG sequences) bind to and activate a set of cell surface Toll receptors (TLR), closely related to Drosophila Toll which performs a similar defense function in insects. The signaling pathway transduced by the TLRs is similar to that triggered by IL-1 receptor itself. Activated TLR recruits myeloid differentiation marker 88 (myd88) to its intracellular region,[10] which in turn recruits IL-1 receptor-associated kinase (IRAK) and TNF-receptor-associated factor-6 (TRAF6).[10,11] TRAF6 activates NFκB, which activates genes involved in the inflammatory response. So far so good.

TRAF6 can bind to RIP2/CARDIAK,[4] although it is not clear that this happens.[5] However, assuming it does (or that a related protein binds to the TLR signaling complex and recruits this adapter), then procaspase-1 can be recruited and activated. In addition, RIP2/CARDIAK also activates NFκB. The binding of procaspase-1 via its CARD

domain activates this caspase, which in turn cleaves pro-IL-1 and pro-IL-18 for secretion.

But here's the problem. Casapse-1 is an efficient activator of procaspase-3, and this should lead inevitably to the death of the cell producing IL-1. However, these same cells are at the forefront of the immune response – monocytes and macrophages phagocytose bacteria and clear them, and can later present bacterial peptides to engage the antigen-specific T cell response. We need these cells to stick around while they are making IL-1. How can they?

First, it isn't completely clear that they do – several reports suggest that IL-1 producing cells undergo apoptosis as they secrete the cytokine. But it seems inherently likely that under real-life situations, the cells can both secrete IL-1 *and* survive. This would require a very careful control of activated caspase-1, allowing just enough activity to process the cytokine, while restricting access to the executioner caspases. Fortunately, we now have two excellent candidates for such control of caspase-1 activity. We think we can expect more.

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