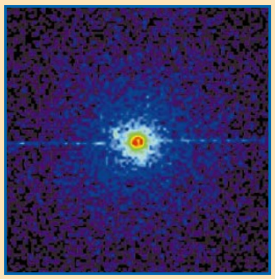
X-ray astronomy

How far to the cosmic lighthouse?



Determining distances to cosmic objects is a challenging business. Most techniques give only relative distances. X-rays detected by the Chandra space telescope from a star in our Galaxy provide a direct way to measure distances to galactic objects, and perhaps even other galaxies.

The star shown in red, Cygnus X-3, is a variable source of X-rays whose emission varies over a period of 4.8 hours. Interstellar dust scatters the X-rays by varying amounts, leading to a 'halo' of radiation. By measuring the difference in arrival times between radiation from the inner halo (green ring) and outer halo (blue ring) a team of astronomers, led by Peter Predehl of the Max-Planck Institute in Garching, Germany, has worked out the distance to Cygnus X-3 to be 30,000 light years.

The uncertainty in the new measurement, to be published in the journal *Astronomy and Astrophysics*, is 20%. The accuracy was limited by the short observation time (3.5 hours) and the authors hope to improve this by observing the star over the whole of its 4.8-hour cycle.

The consequences of this work may be far greater if the technique can be applied to variable X-ray sources in other galaxies. In particular, the distance to the Large Magellanic Cloud is crucial for estimating the age and expansion rate of the Universe, but there has to be enough dust around to produce a useful halo. **Sarah Tomlin**

Recognition and removal of an apoptotic cell by macrophages — a type of phagocyte — is mediated by changes in the expression of membrane-associated markers on the dying cell[2]. These markers selectively interact with specific receptors on the surface of the phagocyte. One common feature of late-stage apoptosis is exposure of the lipid phosphatidylserine, normally localized to the inner leaflet of the plasma membrane, on the outer-membrane leaflet of dying cells. This allows the uptake of dead cells by at least some types of phagocyte[3].

It was assumed that a phosphatidylserine-specific receptor on the surface of the phagocyte must mediate these events, but candidate receptors failed to distinguish between phosphatidylserine and other lipids (something we know the phagocytes do). Now, Fadok and colleagues[1] have identified a phosphatidylserine receptor on the surface of activated human macrophages that selectively allows the phosphatidylserine-dependent uptake of apoptotic cells. Significantly, binding of phosphatidylserine to its receptor triggers the release of anti-inflammatory cytokines (such as transforming growth factor-β) and inhibits the production of pro-inflammatory cytokines (such as tumour necrosis factor-α), providing a link between the recognition of apoptotic cells and the physiological consequences of their uptake.

But the influence of dead cells on vertebrate physiology extends beyond the generation of pro- and anti-inflammatory cytokines[4]. The function of a phagocyte called a dendritic cell can be dramatically affected by both apoptotic and necrotic cells. However, the responses of the dendritic cell to these two stimuli are very different, and this may be one important basis for the ability of the immune system to respond to foreign, but not self, antigens[5,6].

Dendritic cells can engulf and degrade the proteins of target cells, which might be, for example, apoptotic cells resulting from normal tissue wear-and-tear, or necrotic cells following a viral infection (Fig. 1). The peptides generated from protein degradation are displayed on the surface of the dendritic cell by way of the major histocompatibility complex (MHC). These MHC–peptide complexes form the ligands for antigen receptors on T cells, which fight infection. In this way, MHC–peptide complexes regulate T-cell activity.

Uptake of necrotic cells by dendritic cells results not only in presentation of peptides on the cell surface, but also in activation of the dendritic cell to express co-stimulatory molecules[7], which are necessary for T-cell activation and induction of an inflammatory response. In contrast, apoptotic cells do not trigger co-stimulator expression, even if they have undergone secondary necrosis following the induction of apoptosis[7]. Without the co-stimulatory molecules, the MHC–peptide complexes tend to selectively inactivate the T cells that recognize them[6].

Dendritic cells that take up apoptotic cells process proteins present in the dead cells and shuttle peptide fragments into their class I MHC molecules, which are then displayed on the cell surface and can be recognized by T cells. This process of 'cross-priming' is remarkable in that, generally, the only peptides that are displayed on class I MHC molecules are those derived from the proteins present in that cell. Cross-priming defies that 'rule', because the dendritic cell presents peptides derived from the apoptotic cell that it has ingested[8].

All of these results link together to offer an explanation for how the immune system discriminates between self and foreign proteins. During normal cell turnover, phagocytes (including dendritic cells) engulf the apoptotic cells and produce anti-inflammatory cytokines (for example, following engagement of the phosphatidylserine receptor, as shown by Fadok *et al.*[1]). Any antigenic peptides presented, through cross-priming, on class I MHC molecules will fail to stimulate a T-cell response because of the absence of co-stimulation. Instead, the MHC complexes (which contain self peptides derived from the apoptotic cells of the organism itself) will selectively inactivate the appropriate T cells, ensuring that immune responses to these self proteins will be eliminated. Any potential low-level inflammation will be dampened by the induced release of anti-inflammatory cytokines[1], to make sure that no immune activation occurs.

But if, for example, viral infection occurs, the situation may be very different. An inflammatory response would be potently induced as a consequence of extensive necrosis and by the cytokines (such as interferons) produced by the infected cells. Under these circumstances, the antigens associated with class I MHC molecules and displayed on the surface of the dendritic cells would include peptides from both the necrotic cells (that is, self antigen) and viral proteins (that is, foreign antigen). Engulfment of necrotic cells and the pro-inflammatory cytokines act together to activate the dendritic cells, which, in turn, stimulate the production of specialized T cells (cytotoxic effector T cells). These cells eventually destroy the virally infected cells. Fortunately, responses to 'self' antigens do not occur, thanks to the inactivation of potentially responsive T cells during the previous 'quiet' periods of normal cellular turnover. So it appears that apoptosis ensures that inappropriate inflammatory responses to self-proteins do not occur.

The work of Fadok *et al.*[1] reinforces the idea that there are key connections linking the uptake of apoptotic and necrotic cells, the balance between immune homeostasis and inflammation, and activation versus tolerance induction in T cells. These mechanisms all function to ensure the efficient generation of specific immune responses when — and only when — they are needed. ■

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