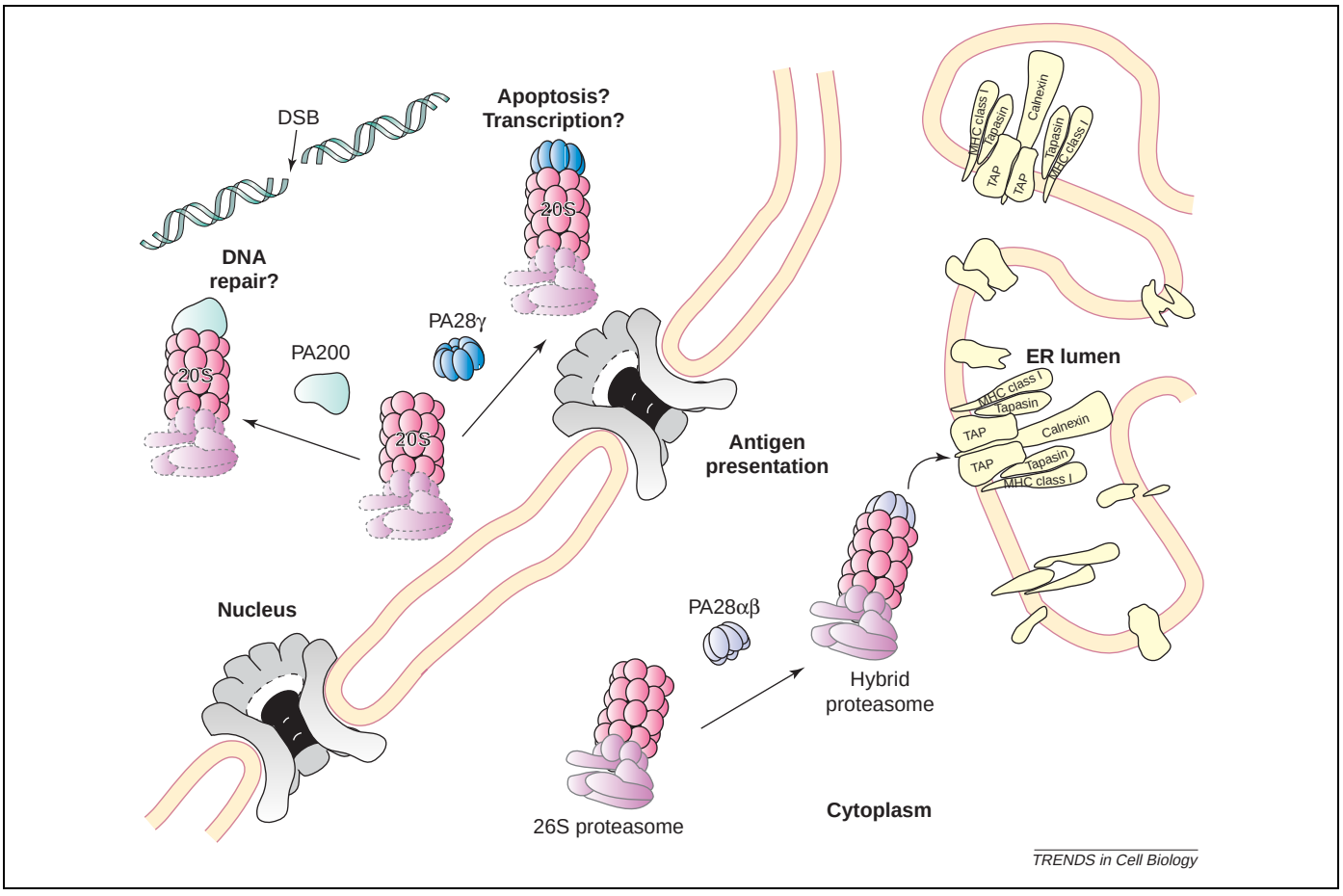


**Figure 4.** Possible biological functions of PA200 and PA28 homologs. PA200 and PA28γ are nuclear and are thought to be involved in DNA repair, and transcription or apoptosis, respectively. In the nucleus, the 19S regulatory complex (PA700) has a broken outline because it is not clear whether PA200 and PA28γ associate with the 26S proteasome or only with the 20S enzyme. PA28αβ is shown in the cytoplasm forming a hybrid proteasome that functions in class I antigen presentation. These properties of PA28αβ are reasonably well established.

epitopes by PA28αβ–proteasome complexes (for review, see Ref. [17]).

Several recent articles reinforce the connection between PA28αβ and cellular immunity. Two groups have reported that mice lacking PA28αβ exhibit impaired class I presentation, although the severity of the immune defects and the proposed reasons for them differ greatly between the two studies. Preckel *et al.* [18] disrupted the *PA28β* gene and observed that the knockout mice, which did not express either PA28β or PA28α, exhibited a general impairment in CTL responses and greatly reduced immunoproteasome levels. They concluded that PA28 is necessary for immunoproteasome assembly and that defects in class I presentation resulted from the lack of immunoproteasomes. In mice, *PA28α* and *PA28β* genes are within six kilobase pairs of each other, which enabled Murata *et al.* to disrupt both of them in a single step [19]. In contrast to Preckel *et al.*, they observed efficient immunoproteasome assembly and normal cellular immunity following influenza virus infection. The $PA28\alpha\beta^{-/-}$ mice were, however, unable to process a specific epitope from the melanoma antigen TRP-2. Murata *et al.* concluded that PA28αβ is not required for immunoproteasome assembly or class I antigen presentation in general but that it is necessary for the presentation of certain epitopes.

Overexpression of PA28αβ in fibroblasts supports the idea that PA28αβ enhances antigen processing independently from any effect on immunoproteasome synthesis [20]. Furthermore, studies of dendritic cells, the professional antigen-presenting cells of the body, showed that immunoproteasome subunits are upregulated early in the maturation process, whereas PA28αβ subunits and many other components of the class I pathway are synthesized later [21]. Thus, it seems unlikely that PA28αβ is involved in immunoproteasome assembly.

Experiments by Yamano *et al.* [22] have addressed how PA28αβ might function in the class I pathway. By examining the presentation of a class I epitope from ovalbumin (OVA) in $PA28\alpha\beta^{+/+}$ and $PA28\alpha\beta^{-/-}$ cells, they found that both heat-shock protein (hsp)90 and PA28αβ enhanced OVA epitope production. The hsp90 inhibitor geldanamycin completely suppressed epitope presentation in $PA28\alpha\beta^{-/-}$ cells, but only partially in $PA28\alpha\beta^{+/+}$ cells. Moreover, when PA28αβ levels were increased in $PA28\alpha\beta^{+/+}$ cells by IFNγ treatment, geldanamycin had no effect on OVA epitope presentation. Because hsp90 is essential for class I presentation when PA28αβ is absent and because it is not needed when PA28αβ levels are elevated, Yamana *et al.* proposed that hsp90 and PA28αβ serve as parallel chaperones that transfer peptides from the proteasome to the class I