Figure 3. Pathogenesis of granuloma formation. (See next page for legend.)
Figure 3. Pathogenesis of granuloma formation. (Legend; see previous page for figure.) (a) Initiation of immune response. Within seconds to minutes after exposure to antigen, resident cells initiate cellular recruitment. Pre-stored tumour necrosis factor (TNF) released by mast cells recruits neutrophils, which in turn signal to and activate tissue and circulating monocytes. Interferon $\gamma$ (IFN-$\gamma$) produced by local natural killer (NK) and $\gamma\delta$ T cells further activates resident tissue histiocytes and dendritic cells. These latter cells release a host of chemokines and TNF, which alter the local microcirculatory environment and facilitate cellular trafficking into the tissue. Within minutes to hours, activated antigen-loaded dendritic cells migrate to peripheral lymph nodes via the lymphatic channels. (b) Production of antigen-specific T cells. Antigen-loaded dendritic cells travel to local lymph nodes and initiate a lymphocytic response. Dendritic cells produce interleukin 12 (IL-12) and present antigen to naive CD4+ T cells. Under the influence of IL-12, naive CD4+ cells differentiate into T helper 1 (Th1) cells. Activated Th1 CD4+ T cells secrete IL-2, which promotes T-cell survival and proliferation, leading to expansion of the population of antigen-specific Th1 cells. (c) Formation of mature granuloma. Within hours to days after antigen exposure, activated Th1 CD4+ T cells preferentially traffic to sites where the microcirculation has been altered by TNF and chemokines produced by resident cells. If the source of antigen is not eradicated, inflammation persists. The interaction between Th1 CD4+ T cells and activated macrophages leads to production of IFN-$\gamma$ and TNF, which results in further maturation of macrophages. Over the course of several days to weeks a mature granuloma is formed. Other cells, including but not restricted to neutrophils and B cells, are found in various proportions in the mature granuloma (see text and references for further details).