From an immunologic perspective, TGF-β possesses broadly immunosuppressive properties and TGF-β knockout mice develop widespread inflammatory pathology and corresponding accelerated mortality (149). Interestingly, a majority of these effects seem to be T cell mediated, as targeted disruption of T-cell TGF-β signaling also results a similar autoimmune phenotype (150). Recent experiments by Chen and colleagues rather convincingly demonstrated a role for TGF-β in Treg-mediated suppression of CD8 T-cell antitumor responses (151). In these experiments, adoptive transfer of $CD4^+$ $CD25^+$ Treg inhibited an antitumor CD8 T-cell effector response, and this inhibition was ameliorated when the CD8 T cells came from animals with a dominant negative TGF-β1 receptor.

One of the unresolved issues in the study of tumor immune evasion relates to the mechanisms by which tumors induce antigen-specific T-cell tolerance. While the many mechanisms described in the preceding text, including STAT3 signaling–dependent mechanisms, IDO, ROS, RNS, TGF-β, etc., clearly inhibit priming of T-cell responses and/or tumor killing by activated effector T cells, it remains to be definitively determined which processes actively induce antigen-specific T-cell tolerance that has been documented in transgenic models. Self-tolerance induction for peripheral tissue antigens is now thought to involve specific presentation of tissue-specific antigens to mature T cells in the absence of appropriate costimulatory signals. Similar mechanisms are likely operative in the case of tumor-induced tolerance. Originally, the relevant costimulatory signals were envisioned to be provided by B7 family costimulatory molecules expressed by DCs (152). It is now becoming clear that additional proinflammatory cytokines such as IFN, IL-12, TNF, etc., are critical in the distinction between effector T-cell induction and tolerance induction.

An emerging concept is that immature or not fully mature DCs are critical in presenting self-antigens to induce T-cell tolerance in the absence of TLR-mediated danger signals associated with infection (153,154). Unquestionably, DCs found within the tumor microenvironment have a relatively immature, unactivated phenotype characterized by low levels of proinflammatory cytokine production and CD86 and surface MHC class II expression. As described earlier, a major inhibitory signaling pathway induced in tumor-infiltrating DC is the STAT3 pathway which, when activated, strongly antagonizes TLR- and CD40-mediated DC activation. As mentioned, tumor-derived factors such as IL-10, IL-6, and VEGF (in part induced by STAT3 signaling in the tumor cell) can induce STAT3 activation in DCs. As described in the previous section, constitutive V-raf murine sarcoma viral oncogene homolog B1 (BRAF), signaling in melanoma cells has additionally been shown to induce release of factors that inhibit DC activation (127). These immature ''activation-inhibited'' DCs clearly represent a prime candidate for the induction of tumor-specific T-cell tolerance.

It remains an open question as to whether iMC/MSC represent a distinct intertumoral cell subset capable of presenting antigens to T cells in a toleragenic fashion (155). A recent report indeed suggested that iMC loaded with antigen and adoptively transferred into mice can induce antigen-specific T-cell tolerance. Finally, it has been suggested that IDO-expressing DC can induce antigen-specific T-cell tolerance because IDO-mediated tryptophan selectively kills or inhibits proliferation of activated T cells (156). According to this model, IDO-expressing DCs would present antigen to T cells inducing activation followed by activation-associated cell death mediated by depletion of local tryptophan stores by the IDO in the presenting DCs. As described in the following text, Treg play an additional important role in induction of or maintenance of tumor antigen-specific T-cell tolerance. Whether Treg mediate T-cell tolerance independently from immature or toleragenic APCs or whether the two mechanisms are completely interrelated (i.e., toleragenic DCs inducing a Treg phenotype among antigen-specific T cells and antigen-specific Treg acting on DCs to enhance their toleragenic capacity) remains to be definitely determined.

DENDRITIC CELLS: THE KEY TARGET OF CANCER VACCINES

The central theme among cancer vaccination strategies is enhancement of modulation of APC function. This is based on the concept that the quantitative and qualitative characteristics of T-cell responses to antigen depend on the signals they receive from the APC. Among the major bone marrow–derived APC subtypes (B cells, macrophages, and DCs), the DC has emerged as the most potent APC type responsible for initiating immune responses (157,158). As described earlier, DCs associated with cancer have altered properties that result in failure to activate T cells optimally. Cancer vaccines in essence seek to skew the function of DCs toward generation of effector T-cell responses.

As virtually all phases of DC differentiation and function can be modulated by engineered vaccines, it is important to understand the molecular signals that regulate their role in activation of T cell–dependent immunity (Fig. 2). At sites of infection and inflammation, bone marrow–derived progenitor cells respond to both proliferative and differentiation signals. GM-CSF, as well as other cytokines such as Fms-like tyrosine kinase-3 ligand (FLT-3L) and IL-4, serve as mitogenic or comitogenic factors that induce an intermediate stage of DC differentiation, characterized by efficient antigen uptake and processing (159–163). Once they have ingested antigens at inflammatory sites in the tissue, immature DCs differentiate in response to a number of distinct ''maturation'' signals. While many diverse molecules induce DC maturation, most appear to signal DCs via binding to two classes of receptor—TLRs and the TNF receptor (TNFR) family. TLRs are ''pattern recognition receptors'' (PRR), which bind common chemical moieties expressed by pathogens termed pathogen-associated molecular patterns (PAMP) such as lipopolysaccharide (LPS) and unmethylated CpG DNA sequences (164). The two best-characterized endogenous DC maturation factors are TNF-α itself and CD40L (165–167). In addition to TLRs, intracellular PRR, including protein kinase R (PKR), RIGI, MDA-5, and NOD1/2, recognize PAMP from intracellular bacteria and viruses that invade the cytosol (126,168,169).

Maturation of DCs, which occurs as they traffic to draining LNs, is characterized by transport of peptide-MHC complexes to the cell surface (170,171). In addition to provision of high densities of peptide-MHC complexes for T-cell stimulation (termed signal 1), DCs regulate T-cell activation and differentiation through provision of costimulatory signals in the form of cytokines, such as IL-12, and membrane-bound ligands of the B7 and TNF family (collectively termed signal 2). The ever-expanding panoply of costimulatory signals utilized by DCs to instruct T cells as to their pathway of differentiation and effector function defines a high degree of complexity to the communications that occur between APC and T cells. When immature DCs present antigens to T cells in the absence of