macrophages. M1 macrophages are activated by the Th1-type cytokine, interferon-gamma (IFN-gamma). M1 macrophages express proinflammatory cytokines, interleukin-12 (IL-12) and IL-23. M2 macrophages are activated by Th2-type cytokines (IL-4, IL-10, and IL-13). M2 macrophages are involved in scavenging cellular debris and in tissue repair.

M2 macrophages can also be immunosuppressive, that is, they can inhibit immune attack against cancer cells (39). Cancer cells express various chemokines, such as **CCL2**, which attracts and recruits M2 macrophages. The recruited M2 macrophages differentiate into immunosuppressive macrophages and, when physically associated with tumors, they are called "tumor-associated macrophages" (TAMs). TAMs resemble M2 macrophages.

The following dwells on the topic of TAMs, and also discloses other techniques that are used by the tumor to evade immune response. Solid tumors are characterized by hypoxia (low-oxygen environment), and energy metabolism in tumors uses anaerobic glycolysis to a greater extent, and oxidative phosphorylation to a lesser extent. Tumor hypoxia was discovered by Otto Warburg (40,41). The hypoxia induces the tumor cells to express various proteins, including **CCL2**, **VEGF**, **EMAPII**, which attract macrophages to the vicinity of the tumor (42). And once attracted the TAMs secrete high amounts of **VEGF** (which stimulates vascularization of the tumors), and also secrete IL-10, an antiinflammatory cytokine (43).

e. Immune Evasion Caused by Activity of T Regulatory Cells

This introduces the topic of T regulatory cells (Tregs). "Tregs" is pronounced, "tee-regs." Tumor-associated macrophages secrete chemokines, such as CCL17, which recruit Tregs to the tumor. Tregs, formerly called suppressor T cells, function to dampen immune response.

Tregs are $CD4^+$ T cells, and they occur in various subsets, including $CD4^+$ $CD25^+$ FOXP3 Tregs, and IL-10-producing Tregs (Tr1 cells) (44,45,46). CD25 and FOXP3 are used as biomarkers for identifying Tregs, and for distinguishing them from other types of lymphocytes. Tregs are beneficial to human health, in that they prevent inappropriate immune response against normal cells in the body, and prevent massive autoimmunity.

This utility of Tregs was dramatically shown by a naturally occurring mutant mouse,

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