Interleukin-1-mediated inflammation and the malignant process

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Interleukin-1 (IL-1) is a pleiotropic pro-inflammatory and immunostimulatory cytokine with diverse effects in steady-state homeostasis and in disease. The IL-1 family consists of two agonistic proteins, namely IL-1α and IL-1β, and one antagonistic protein, the IL-1 receptor antagonist (IL-1Ra), which binds to IL-1 receptors without transmitting an activation signal. In their recombinant form, IL-1α and IL-1β bind to the same receptors and exert the same biological activities. However, in the physiological milieu, IL-α and IL-1β differ dramatically in the sub-cellular compartment in which they are found, which dictates distinct functions. Thus, IL-1α is mainly active as a cell-associated cytokine (cytosolic, nuclear and membrane-associated forms), while IL-1β is active only in its secreted mature form. As a ubiquitous mediator at tumor sites, IL-1 is produced by microenvironmental cellular elements as well as by the malignant cells. Cell-associated IL-1α translocates into the nucleus, especially upon stress, where it binds to chromatin in a dynamic manner. During necrosis of stressed cells, IL-1α is released into the microenvironment and initiates sterile inflammation. However, upon an apoptotic cell death, IL-1α binds avidly to chromatin and is not released from the cells and thus inflammation is not induced. For the propagation of the inflammatory response induced by IL-1α of damaged tissue origin, it synergizes with IL-1β secreted with bone marrow-derived myeloid cells, which results in an extended inflammatory response, characterized mainly by infiltrating mononuclear cells. Also, recombinant IL-1α is dominant in early recruitment of neutrophils, while recombinant IL-1β is more effective in recruiting mononuclear cells, further attesting differential roles to the IL-1 agonists. In the malignant process, extended inflammatory responses related to carcinogenesis, tumor cell invasiveness and tumor angiogenesis were mainly dependent on microenvironment-derived IL-1β which is mainly secreted by infiltrating myeloid cells, with some contribution to tumor cell-derived IL-1. In accordance, treatment of tumor-bearing mice with IL-1Ra or specific anti-IL-1 antibodies alleviated tumor burden. However, host-derived IL-1α, which is mostly cell-associated, is dominantly involved in the process of craving the immunogenic repertoire of the malignant cells in the process of immunoediting. Furthermore, IL-1 was shown to be a major cytokine, which affects the balance between the chronic wound-healing type of inflammation, which is involved in tumor progression, and activation of professional APCs in a limited inflammatory milieu, which leads to induction of anti-tumor cell immunity and reduction of the tumor burden. Better understanding the circumstances by which molecules of the IL-1 family affect the malignant process will broaden the use of IL-1 manipulation in tumor therapy.