New Developments: A Look to the Future
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Inflammatory cytokines plus the human immunodeficiency virus Tat protein apparently trigger the development of early Kaposi's sarcoma. Activated spindle cells provide a self-perpetuating, autocrine-supported mechanism for further development of hyperplastic lesions. In more advanced stages, a true neoplastic process may develop. [ONCOLOGY 10(Suppl):34-36, 1996]

Introduction

Kaposi's sarcoma (KS) is of special interest not only because of its association with the epidemic of human immunodeficiency virus (HIV) infection (AIDS-KS), but also because studies of its pathogenesis appear likely to contribute to a deeper understanding of tumor biology, particularly angiogenesis. This is true despite a major paradox: researchers are still uncertain as to whether or not the four types of KS actually represent a single disease and even whether or not KS, which can certainly produce tumors, is a true neoplasm.

Neoplasia or Hyperplasia?

KS tumors are characterized by a significant complexity of cell types. Many normal cells infiltrate into the mass generally referred to as the KS lesion [1-3]. Furthermore, in most patients with this disorder, it remains difficult to prove that there are truly clonal, proliferating, malignant cells at any time. Our group and another group from Israel have established KS cell lines that are truly neoplastic; our tumor cell line (KS Y-1, derived from AIDS-KS) [4] produces metastatic disease in mice, whereas the other cell line (derived from a patient with classic KS) is tumorigenic but not metastatic [5]. However, these lines are derived from cells that appear to be quite rare in KS lesions, because many attempts have been made to establish cell lines from other cell types, with no success. Another possibility, which most likely accounts for the majority of KS lesions, is that the significant event may be hyperplasia-induced and maintained by the spindle cell, which secretes or releases cytokines that permit infiltration and proliferation of other cell types [6-10]. Our work has focused on characterizing cells from KS lesions in terms of the phenotype and cytokines they secrete and their ability to create model KS lesions when inoculated into nude mice. We have demonstrated that most of the KS spindle cells that clearly were not neoplastic [11,12] have the same phenotype as that of most of the in situ spindle cells [2,13] and can produce a lesion in mice that is histopathologically indistinguishable from early KS [11,12]. The multifocal nature of this tumor raises the question of whether this could be hyperplasia, rather than neoplasia, at least in its early stage. If so, the abnormal milieu of HIV-infected individuals may be permitting an increased local proliferation of a variety of cell types, depending upon the local environment. If this is the case, the spindle cell may have become seeded in the blood and disseminated to sites where it can reside and induce local inflammation-like changes. Neoplastic conversion may be a chance late-stage phenomenon.

Characteristics of the KS Cell

Culture of cells from primary biopsy specimens of patients with KS is achieved by using conditioned media from activated T-cells [11,14,15]. These cells have a spindle-shaped morphology and an activated endothelial-cell phenotype that is identical to that of most in situ spindle cells [2,13]. Conversely, normal endothelial cells grown in a medium that contains inflammatory cytokines from activated T-cells give rise to a similar or identical type of spindle-shaped cell [13,16]. In both cases, these cells have receptors for a great number and variety of cytokines. The predominant cytokines involved in producing this activated cell are interleukin-1 (IL-1), tumor necrosis factor, and gamma
interferon. Of importance, these cytokines are the same inflammatory cytokines increased in KS lesions (B.E., unpublished data, 1995).

Once activated in this way, the spindle cell then proliferates and produces its own cytokines in very large amounts. This is particularly true of basic fibroblast growth factor (bFGF), which is not released in significant amounts by normal cells [6]. The KS spindle cells have receptors for bFGF and produce and release more bFGF than any other known cell both in vitro and in vivo [6,17,18]. Basic fibroblast growth factor is also highly expressed by in situ spindle cells of both classic KS and AIDS-KS lesions, inducing autocrininic KS cell growth. Upon release, bFGF promotes angiogenesis and KS-like lesions that are indistinguishable from those induced by KS spindle cells or lesions induced by cytokine-activated endothelial cells [6,17-19].

The spindle cell also produces vascular endothelial cell growth factor, platelet-derived growth factor, IL-6, granulocyte-macrophage colony stimulating factor (GM-CSF), and IL-8 [6,8,9,20]. Some of these cytokines also serve an autocrine function in keeping the spindle cell functioning. The most important factor, however, appears to be bFGF, because most spindle cell growth can be blocked by polyclonal antibodies to bFGF or antisense oligodeoxynucleotides directed against bFGF [6,17].

The derivation of the KS spindle cell has been recently elucidated. Most of the current findings indicate a microvascular endothelial origin in an activated state [2,3,13]. Cultured spindle cells do lack the vascular endothelial cell marker FVIII-RA; however, this molecule is released in the presence of inflammatory cytokines. In fact, when KS cells are cultured in their absence, the expression of this molecule is regained [13]. In addition, these cells present other specific endothelial cell markers, such as CD34, Chaderin-5, and ELAM-1 [2]. Other spindle-shaped cells present in patients with KS are macrophages/dendritic cells [2,19].

Circulating vascular endothelial cells can be found in normal persons, but circulating spindle cells are very uncommon. In fact, the numbers in normal persons are so low that we have been unable to characterize fully these cells in that population [21]. In patients with HIV-related KS, spindle cells are 85-fold more common in peripheral blood. In most HIV-infected patients who do not have KS, spindle cell numbers are nearly the same as those in control patients [21]. In HIV-infected homosexual men, however, spindle cell numbers are nearly 20-fold higher than in controls [21]. These differences in cell numbers may have some clinical importance, if they can be used to monitor response to therapy or progression of KS.

Development of KS Lesions from Spindle Cells

KS-like lesions can be produced in nude mice by inoculating them with spindle cells [11,12,17]. The tumor produced is of mouse origin, which is grown in response to cytokines secreted by the human cells. A medium that is conditioned by spindle cells has the same effect. This suggests that the spindle cell, regardless of whether it is neoplastic or not, may be driving the KS lesion from early stages. In particular, bFGF appears to be the major mediator of these lesions [17,19], although recent data suggest that vascular endothelial cell growth factor can amplify the angiogenic response to bFGF (F. Samaniego, md, unpublished data, 1995).

Contribution of the Tat Protein

The HIV transactivator (Tat) protein, which is released from acutely infected T-cells, probably by a process of exocytosis, also plays an important role in the development of KS [22]. It not only increases KS spindle-cell growth, but also induces the migration, invasion, and adhesion of KS cells and cytokine-activated endothelial cells [13,16,22-24]. Most important, the Tat protein is synergistic with bFGF in inducing angiogenesis and KS lesion development [19]. We also know that normal endothelial cells are not responsive to the Tat protein unless first exposed to inflammatory cytokines [13,16,22-24]. The Tat protein is detected in AIDS-KS lesions, and it co-stains with the integrin receptors alpha 5/beta 1 and alpha V/beta 3, which function as the receptors for this protein [19,24]. In fact, the Tat protein appears to mimic the effect of the extracellular matrix protein, the natural ligands of these receptors [24]. By these effects, the Tat protein may be the factor increasing the frequency and aggressiveness of KS in HIV-1-infected individuals.

New Infectious Agents

Many infectious agents have been associated with KS; however, only recently has a definitive link with an infectious agent other than HIV-1 been found. Specifically, recent data indicate that a novel herpesvirus is detected in all forms of KS [25,26]. This virus, called KS-HV or HHV-8, has also been
found in a subtype of AIDS-associated B-cell lymphomas [27] and in peripheral blood mononuclear cells from KS [28] but not in KS spindle cells representative of both the hyperplastic and tumor phases of KS (S. Colombini, md, unpublished data, 1995). Although there is no evidence that this virus causes KS, it is possible that it may initiate inflammatory cytokine production in infected cells within the lesions and may trigger the mechanisms of KS development.

The recent evidence of this virus, however, does not explain the elevated rates and aggressiveness of KS in HIV-infected homosexual men, compared with the rates in other HIV-infected groups, as in the normal population, which continues to puzzle epidemiologists and clinicians alike. In fact, HHV-8 is present in all forms of KS with about the same prevalence. The production of spindle cells in response to exposure to inflammatory cytokines suggests that these cell messengers are implicated. We know from our own laboratory studies that inflammatory cytokines can cause endothelial cells to become activated and detach, which would enable them to enter the circulation, and that in HIV-1-infected individuals, the Tat protein may increase KS development and progression. An increase in inflammatory cytokine levels [28-31] and the presence of the extracellular Tat protein in AIDS-KS, coupled with the results of our in vitro studies, clearly show that inflammatory cyto-kines from activated T-cells induce activated spindle cells, which begin to proliferate and assume many of the characteristics associated with KS lesions.

Conclusions

The evidence strongly suggests that inflammatory cytokines, perhaps produced after infection with HHV-8, plus the HIV Tat protein trigger development of early KS. Development of activated spindle cells, apparently derived from microvascular endothelium, provides a self-perpetuating, autocrine supported mechanism for further development of the hyperplastic lesion. In more advanced stages, a true neoplastic process may develop.

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