A connection between metastatic cancer and cachexia has been recognized for centuries. Yet a clear understanding of the mechanism that links metastasis and cachexia has been lacking. Recent results—using an IL-1α antagonist—show for the first time reversal of cachexia in metastatic cancer. These results offer hope to patients, and new insights into understanding the mechanism behind cancer cachexia.

A body of experimental and clinical evidence has for some time underscored the importance of tumor-platelet interactions in the growth and metastasis of tumors. While the mechanism of action for the anti-IL-1α therapy in the treatment of cachexia has not been formally established, recent work revealing large amounts of IL-1α on the surface of platelets is pointing towards the involvement of platelets in mediating cachexia. The discovery of IL-1α on platelets sheds new light on the possible mechanism by which platelet-tumor cell interactions could mediate actions to deregulate energy balances, leading to chronic utilization of muscle as a fuel source and resulting in the severe muscle atrophy seen in cachexia.

IL-1 signaling in the hypothalamic-pituitary-adrenal (HPA) axis has been implicated in central nervous system (CNS) dysregulation of energy and muscle metabolism. The outcome of IL-1-driven CNS disturbances, particularly in the hypothalamus, have been shown to cause appetite suppression and metabolic changes consistent with cachexia. Yet the source of IL-1 stimulation in the brain has been unclear.

A most basic definition of inflammation is the movement of leukocytes across the blood-tissue barrier. The vascular endothelium acts as the barrier to restrict leukocyte transit into tissue. In turn, regulation of cellular transit across the vascular endothelium—and thus the control of inflammation—is orchestrated by leukocytes themselves.

Interaction between platelets and the vascular endothelium is crucial in regulating the activation of the endothelial cells—and thus in regulating inflammation. The most numerous cell in the blood, and marginated in the blood flow along the vessel wall, platelets are highly interactive with the vascular endothelium. Through interaction with the vessel wall, platelets can act as a first step in the activation of vascular endothelial cells and thereby help to regulate the migration of leukocytes from the blood into tissue. The ability to exert control over the vascular endothelium, with respect to transendothelial migration, is a highly adapted feature of platelets. Platelets have numerous surface molecules and secreted moieties to enable these specialized interactions and functions. Thus part of the complex function of platelets (besides hemostasis) is to play a unique role in orchestrating and regulating the egress of leukocytes from the circulation into tissues.
Figure 1.11  Platelets are marginated in the blood flow, allowing enhanced interaction with the vascular endothelium. Platelets are highly adapted to interact with—and regulate the activatory status of—vascular endothelial cells. Illustration depicts blood cells flowing through an artery. Platelets (white arrow) are traveling next to the vascular endothelium (green arrow). Red blood cells and leukocytes mainly flow in the higher velocity axial, or central stream of the blood flow.

Tumor cells, on the other hand, inherently lack all the specialized functions that platelets use to interact with, and activate, the vascular endothelium. Thus most tumor cells are not able to facilitate cellular migration into tissues. There are numerous specialized molecules and functions engendered by platelets to enable their role in communicating with the vascular endothelium and regulating transendothelial migration. It is difficult to conceive how tumor cells might spontaneously develop these attributes of the platelet necessary for controlling migration across the vasculature. Yet, in metastatic disease, tumor cells have successfully transited the blood stream and undergone transendothelial migration to form new sites of metastasis.

Rather than performing the task of priming the vascular endothelium to permit transendothelial migration, it is much simpler to imagine how tumor cells might develop the ability to induce the platelet to do the job for them. It might be expected, therefore, that in the context of metastatic disease, tumor cells will have emerged with the ability to co-opt platelets in their role as regulators of transendothelial migration. There is thus the potential for platelets to play a crucial role in cancer metastasis.¹
The idea that platelets play a role in metastasis and malignancy is not new. As early as 1878, the German surgeon Theodore Bilroth was lecturing medical students at the University of Vienna on the relationship between tumor-platelet aggregates and the spread of cancer. Dr. Bilroth’s hypothesis has been confirmed numerous times since, both clinically and experimentally, and there have been ongoing advances in understanding the mechanisms and molecular events involved in tumor-platelet interactions, as well as how these events conspire to activate the vascular endothelium and support extravasation.

The platelet’s role in the spread of tumors via the blood involves a crucial step: the formation of so called tumor-platelet “microemboli”. Tumor-platelet aggregates represent what is in essence tumor cell “hijacking” of the platelet’s ability to interact with vascular endothelium.

Tumor-platelet interactions have been shown to be sufficient and in many cases necessary to facilitate metastasis. In 1953, Lawrence et al. showed that a pretreatment with heparin was 100% protective in rabbits injected with what was otherwise a lethal metastatic carcinoma¹. Myriad animal models and numerous clinical observations have reconfirmed over decades this deadly dynamic between tumors and platelets. ²,³,⁴
While the role of tumor-platelet interactions in metastasis has been convincingly demonstrated, the role of metastasis in progression of cachexia has remained an enigma. In the 1980 landmark publication by the Eastern Cooperative Oncology Group (ECOG), it was revealed that any amount of cancer-associated weight loss correlated with dramatic reduction in survival\(^1\). This was true for virtually all forms of cancer. Moreover, it was observed that for the large majority of patients, the presence of only a single identified metastatic lesion was highly correlated with weight loss. The conclusion was clear: metastasis and weight loss—i.e. cachexia—are inextricably linked. The ECOG study was groundbreaking because of the collaboration of so many experts, and because of the excellence of the reported data. The relationship between metastasis and cachexia was irrefutable. Thus for the past 30 years, a crucial undertaking has been to solve the enigma of metastasis in cachexia.

Answers to this deadly puzzle have recently come from elegant studies that identified the role of the CNS in regulating energy balance and muscle catabolism. The role of inflammatory cytokines (and in particular IL-1 signaling) in the hypothalamus has become a central theme in this work. What has emerged is a detailed elucidation of the different efferent neuronal pathways emanating from the arcuate nucleus of the hypothalamus to regulate appetite, muscle catabolism and weight loss. The recent discovery of dynamic interleukin IL-1 receptor expression on cells of the arcuate nucleus suggested a key role for the cytokine in mediating the effects of cachexia. Animal studies have demonstrated that IL-1 is in fact a crucial mediator of the metabolic syndrome.

Although the role of IL-1 signaling in the CNS has been established, the connection between tumor metastasis and cachexia has remained elusive. In the absence of metastasis in the hypothalamus itself, and with negligible levels of IL-1 in the serum, how during metastasis might the effects of IL-1 inflammatory signals get generated in this subregion of the forebrain?

An answer comes from the recent identification of significant levels of IL-1α on platelets, providing a plausible “missing link” between tumor metastasis and cachexia.

As illustrated in Figure 1.14, tumor adherence to and activation of platelets facilitates the formation of tumor-platelet aggregates that interact with the vascular endothelium. Vascular endothelial cells constitutively express the receptor for

**Figure 1.13** Tumor-platelet interactions play an essential role in metastasis. Images show melanoma metastasis to the lung in a murine model. Almost complete abrogation of metastasis is seen in mice depleted of platelets (left panel). Mice were injected with B16F10 melanoma cells, and their lungs were examined after 14 days. An intact platelet compartment results in extensive metastasis (right panel). Treated animals underwent antibody-mediated platelet depletion prior to infusion of melanoma cells (Erpenbeck and Schon, 2010).
interleukin-1 alpha (IL-1R). The arrest of tumor-platelet microemboli on the vascular endothelium results in platelet-bound IL-1α interaction with the IL-1R receptor on endothelial cells. These interactions in the microvasculature of the arcuate nucleus can explain the source of IL-1 signaling that has been associated with cachexia.

Platelet-derived IL-1α signaling between tumor-platelet microemboli and the vascular endothelium in the brain provides a direct connection between metastatic disease and cachexia. The adherence of microemboli in the vasculature of the hypothalamus—likely the postcapillary venules—enables platelet-associated IL-1α activation. This signaling could therefore occur in the presence or absence of extravasation of tumor-platelet emboli into the hypothalamus, and thus in the presence or absence of an evident inflammatory process in the CNS. The interaction of microemboli in the region of the arcuate nucleus could thus provide a mechanism by which metastasis—and IL-1α—can trigger CNS dysregulation of the energy metabolism, appetite suppression and muscle loss in cachexia.

![Figure 1.14](image.png) IL-1α on the surface of platelet-tumor microemboli stimulate IL-1 receptor (IL-1R, purple projections) on vascular endothelial cells. By this mechanism, recirculating micrometastasis can trigger IL-1 inflammatory signals in the vasculature. Illustration shows cells flowing through a blood capillary vessel. Platelets (small blue cells) bearing IL-1α (red spots) are interacting with IL-1R on the surface of vascular endothelium. This interaction is taking place in the context of platelets that have been activated after binding to tumor cells (brown figures). IL-1R activation in the vasculature of the hypothalamus can transduce signals causing cachexia.

The discovery of significant levels of IL-1α on platelets (and platelet microparticles) points towards a crucial role for this cell-surface cytokine in pathophysiological inflammation. By targeting IL-1α with a non-depleting antibody, it is possible to block a crucial stage of the inflammatory process—movement of circulating leukocytes across the blood-tissue barrier. This mechanism thus provides a means to undermine tumor potential by blocking leukocyte-driven processes, such as tumor stroma remodeling, neo-angiogenesis and metastasis.

The interaction of tumor-platelet emboli in the microvasculature of the brain solves the riddle of how the induction of IL-1 signaling in the brain occurs in the absence of soluble IL-1 in the plasma. It also provides the link between metastasis and cachexia.


