qualities can be described as myeloid-derived suppressor cells (MDSCs).7

Despite major differences in their ontogeny, lineage, and differentiation stage, the players in both groups share fundamental similarities. First, all are functionally plastic because the microenvironment to which they are exposed determines their inflammatory profile. Second, the mechanisms underpinning their immunosuppressive activity often involve amino acid metabolic pathways and oxidative stress.7,9 Finally, as a downstream effect, most of these cellular pathways have the ability to activate Treg.

Now Zhang et al report that fibrocytes are a new player in the cancer-associated “innate tolerance” network. Fibrocytes, a cell subset of hematopoietic origin with fibroblast markers and morphology, had so far been considered inflammatory cells with a prominent role in the genesis of fibrosis.10 This study describes their potential role in effecting tumor evasion. The authors found increased numbers of circulating fibrocytes (CD14+CD11c+CD123+) in patients with metastasis. These fibrocytes expressed a phenotype resembling the one of MDSCs (CD11b+CD15+CD66b+IL4Rα), but relatively distinct because of the high expression of HLA-DR and mesenchymal markers. Circulating fibrocytes from the patients, but not from normal individuals, exhibited immunosuppressive and proangiogenic activities, thus strongly suggesting the case for tumor-induced polarization and a further mechanism in tumor evasion from immune surveillance. Such a notion is consistent with the observation that fibrocyte differentiation decreases in inflammatory conditions and tissue injury, whereas it increases under conditions associated with wound healing and tissue remodeling.

Although not investigated in the study, it seems plausible that the nature of the “licensing” signals required for immunosuppressive fibrocytes (F2) are similar to those described for suppressors of myeloid or mesenchymal origin, such as tumor necrosis factor-α, interferon-γ, and the hypoxic tumor environment. The authors convincingly demonstrate that IL-4 can generate F2 in vitro, but the actual contribution of the tumor to their formation remains to be elucidated. It is also unknown whether fibrocytes at the tumor site exhibit the same characteristics of the circulating fibrocytes. A further similarity with the other suppressors is the mechanism of action. As with MSCs and tolerogenic DCs, fibrocytes use indoleamine 2-3-dioxygenase (IDO), which depletes the cellular microenvironment of the essential amino acid tryptophan, required for T-cell proliferation. The authors failed to detect any of the pathways involved in MDSC-mediated immune inhibition (arginase or nitric oxide), but this may depend on the cancer type, which may activate selective pathways only. Further analysis of the immunosuppressive molecules will unravel additional, potentially overlapping, mechanisms such as inhibitory cytokines (IL-4, IL-10, IL-13) and the ability to induce Treg.

A question stemming from this study is whether fibrocytes, MSCs, and MDSCs are unique entities or whether they instead reflect a functional status—elicited by inflammation or tumor environment—that can be acquired by cells of different origin that have in common the machinery to activate innate pathways of immunosuppression. What we have learned from the characterization of the MDSC subsets suggests that tumor conditioning is more complex than a simple polarizing process, because each subset responds differently, and the same effector molecule can mediate different activities when it is secreted by different subsets.

From a translational perspective, the findings by Zhang and colleagues might add discouragement in regard to tumor immunotherapies because of the apparent need to control a new population. However, the evidence that tumor-associated fibrocytes use a well-known weapon (IDO) in the armamentarium of innate tolerance suggests that tumor can teach a new dog, but only old tricks.

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**References**


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**CLINICAL TRIALS & OBSERVATIONS**

Comment on den Exter et al, page 1144

**Importance of subsegmental pulmonary embolism**

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In this issue of Blood, den Exter et al highlight the importance of subsegmental pulmonary emboli.1

Pulmonary embolism (PE) causes 100 000 or more deaths each year in the United States2 and is the primary diagnosis or a complicating condition in more than 300 000 patient hospitalizations.3

The diagnosis of PE has been revolutionized with the introduction of advanced computed tomographic pulmonary angiography (CTPA).4 The multi-row detector CTPA is highly sensitive and specific.

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for PE, including the relatively smaller emboli confined to subsegmental pulmonary arteries. Consequently, the proportion of all emboli diagnosed in symptomatic patients that are confined to subsegmental arteries has increased from 4.7% with the single detector to 15% with multi-row detector CTPA. A recent systematic review has suggested that this improved detection of subsegmental PE represents overdiagnosis of relatively unimportant emboli for which the risks of anticoagulant therapy may not be warranted.

Now come den Exter and colleagues with important new data that strongly challenge this inference. These investigators used the combined data from 2 large prospective cohort studies of patients with clinically suspected PE, to compare the thromboembolic risk profiles and clinical outcomes of patients with subsegmental PE by CTPA (116 patients, 15.3%) with those of patients with segmental or more proximal emboli (632 patients) and with those in whom PE was ruled out (2980 patients) on the basis of either an unlikely clinical probability combined with a negative D-dimer result or by negative compression ultrasonography in the lower extremities. The methodology was strong, and follow-up for 3 months was complete in 99.8% of patients. The most important findings concern the outcomes on follow-up. Among the 116 patients with subsegmental PE, all of whom received anticoagulant therapy, symptomatic recurrent venous thromboembolism occurred in 4 patients (3.6%). In contrast, only 1.1% of the 2980 patients in whom PE was ruled out and who did not receive anticoagulant therapy had symptomatic venous thromboembolism on follow-up (hazard ratio for subsegmental PE, 4.3; 95% confidence interval 1.5-12.3). There was a gradient for mortality, which was highest among patients with segmental or more proximal PE (10.7%), followed by subsegmental PE (6.5%), and lower in patients in whom PE was excluded (5.4%, P = .01 compared with patients with subsegmental PE).

How do we reconcile these results with the prior systematic review? Two facts are relevant. First, the studies that suggest that subsegmental PE does not require anticoagulant therapy all included imaging for deep-vein thrombosis using ultrasonography to detect and treat those patients with this source for recurrent embolism. The presence of deep-vein thrombosis is a key prognostic marker for recurrent venous thromboembolism and an independent predictor of mortality among patients with PE. Imaging for deep-vein thrombosis is therefore “…an important component of the management of subsegmental pulmonary embolism left untreated.” Second, den Exter and colleagues show that patients with subsegmental PE have persistent risk factors for recurrent venous thromboembolism, and these risk factors occur less commonly among the patients in whom PE was ruled out. The significant prevalence of active malignancy (18%) helps to explain the 3.6% incidence of recurrence despite anticoagulant therapy.

What are the implications for current clinical practice? A symptomatic patient with confirmed subsegmental PE who does not have an absolute contraindication or risk factor(s) conferring a high risk of bleeding should be treated with anticoagulant therapy unless strong patient preference dictates otherwise. The safety and simplicity of anticoagulant therapy have been improved with the new oral anticoagulants. This development, together with the data of den Exter et al., tips the balance in favor of anticoagulant therapy for most patients. In patients with absolute contraindications or a high risk of bleeding, serial imaging for deep-vein thrombosis of the legs using compression ultrasonography is likely a safe alternative, providing several conditions are met: (1) the patient has adequate cardiopulmonary reserve to tolerate the existing embolus left untreated and/or a small recurrent embolus; (2) that ultrasonography can be done 3 or 4 times over a 10- to 14-day period to detect a new proximal deep-vein thrombosis before it leads to important recurrent PE; (3) that persistent risk factors for recurrent venous thromboembolism are absent; and (4) that alternate sources for recurrent PE are absent (eg, central venous catheterization). The ongoing prospective cohort study (NCT 01455818) of withholding anticoagulant therapy in patients with subsegmental PE who have negative results by serial ultrasonography for deep-vein thrombosis is awaited with interest. For now, PE, including subsegmental PE, should be considered a serious and unforgiving condition for which the benefits of contemporary anticoagulant therapy outweigh the risks for most patients.

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