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COMMENTARY

Absence of PAF actions increases angiogenesis

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Conventional medical knowledge predicates that inflammation and angiogenesis are closely associated phenomena. For decades, angiogenesis, previously described as erythema or redness, has been viewed as one of the cardinal signs of inflammation, the two phenomena being inextricably interwoven. This firmly established notion has been challenged by the discovery of mediators of inflammation endowed with a wide repertoire of angiogenic actions ranging from potent stimulators to suppressors of angiogenesis. The most cogent examples of molecules, which may exert opposing actions on angiogenesis, while invariably contributing to inflammation, are found in the interleukin and cytokine class of mediators (Cozzolino *et al*., 1990; Szekanecz & Koch 2001; Hatzi *et al*., 2002). For example, IL-1, IL-6 and IL-10 exert both angiogenic and angiostatic action depending on the experimental conditions (Cervenak *et al*., 2000; Kohno *et al*., 2003; Wei *et al*., 2003; Bar *et al*., 2004). Thus, the relationship between inflammation and angiogenesis appears less unequivocal than previously thought. Reports on tumor angiogenesis and the prognostic significance of the inflammatory infiltrate are a good example of conflicting evidence (Griffioen *et al*., 1996; Offersen *et al*., 2002). Certainly the extrapolation of observations in isolated cell populations to *in vivo* experimental models designed either for inflammation or angiogenesis contribute to the ambiguity on angiogenic properties of inflammatory mediators (Gullino, 1981; Auerbach *et al*., 2003).

In the current issue of the journal, Ferreira *et al*. (2004) have revisited the role of endogenous PAF in chronic inflammation, in angiogenesis, and other sequela of inflammation such as cell recruitment and in the production of cytokines. To study endogenous PAF, they used either PAF receptor-deficient mice (PAFR-KO) or wild-type mice orally treated with a PAF receptor antagonist. Chronic inflammation was induced by a sponge implant, a condition that promotes granolomatous tissues closely reproducing that occurring in human pathology. In the study of Ferreira *et al*. (2004), the absence of the effects of endogenous PAF induced a significant stimulation of angiogenesis, and attenuation of the inflammatory response. This finding sharply contrasts with a wealth of literature data describing the abundance of PAF, rather than its absence, as a potent stimulus for the activation of endothelial cells leading to the formation of new vessels (Brizzi *et al*., 1999; Montrucchio *et al*., 2000; Deo *et al*., 2002). However, the portrayal of PAF as a proangiogenic molecule has been drawn from *in vitro* experiments on cultured endothelial cells exposed to exogenous PAF (Brizzi *et al*., 1999), or from *in vivo* studies in which angiogenesis was inherently primed by matrigel implants (Montrucchio *et al*., 2000), or a combination of PAF and angiogenic stimulator (Montrucchio *et al*., 2000). An emerging concept is that the extent of angiogenic response greatly depends on the innate angiogenic tone. Thus, it appears that the activity of PAF, a ubiquitous lipid mediator of inflammation, is strongly influenced by the experimental conditions giving rise to opposing effects.

The decreased inflammation observed by Fereira *et al*. (2004) in PAFR-KO mice was accompanied by a reduced level of inflammatory cell infiltrate and no modification of known angiogenic factors such as VEGF and TNF-a, but unexpectedly by a sustained rise of chemokines CXCL2 (KC) and CCL2 (MCP-1/JE). The enhanced level of these chemokines indicates that loss of PAF's effects does not indiscriminately suppress all inflammatory signals, which perhaps compensates for the absence of an important molecule in maintaining immunogical surveillance. Moreover, the elevation of CCL2 (MCP-1/JE), particularly significant in PAFR-KO mice, may account for the increased vascularization, since this cytokine possesses consistent proangiogenic activity (Goede *et al*., 1999).

In summary, the article by Ferreira *et al*. (2004) contributes to the better definition of the role of PAF in inflammation and in angiogenesis in conditions that mimic mild chronic inflammation in man. PAF appears to be a physiological mediator of inflammation, which negatively regulates angiogenesis rather than promoting it, a profile that is also shared by other mediators of inflammation. In physiological angiogenesis the interplay among endogenous stimulators and inhibitors, although highly redundant, is tightly regulated to achieve neovascular growth in maintaining tissue integrity. While some molecules have been selectively assigned to either function, others have been shown to possess opposing actions. Whether PAF belongs to the latter class of molecules, as suggested by the report of Ferreira *et al*. (2004), needs to be substantiated in other models.

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