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The role of Angiopoietin2 in blood–brain barrier breakdown and angiogenesis

The advent of effective chemotherapy and more recently of targeted therapy has made significant difference in the treatment of metastatic disease to the brain. The successes of these forms of therapy have served to highlight certain lacunae in our knowledge of pathophysiologic processes. One of these areas is the blood–brain barrier, which selectively blocks access of (good and bad) molecules to the brain. Recent data shows that Angiopoietins (Ang) 1 and 2 play a major role in angiogenesis in the brain and may be involved in the control of *trans*-endothelial migration of molecules. *In vitro* studies have shown that Ang1 is antiapoptotic, while Ang2 is proapoptotic in the endothelium. However, it has been suggested that in the presence of vascular endothelial growth factor (VEGF), Ang2 paradoxically destabilizes blood vessels and induces angiogenesis. **Zhu *et al***[1] used an adenovirus vector system in a mouse model to analyze the importance of the combination of VEGF and Ang2 to angiogenesis. Transfected mice with adenovirus vector carrying Ang2 and concomitantly treated with intraventricular infusion of VEGF-A showed significant increase in microvessel density. The combination of VEGF and Ang2 promoted angiogenesis to a greater degree than either agent by itself. The authors also observed induction of matrix metalloproteinases (MMP-9) and alterations in polarity of the endothelial cells, and suggested that these might lead to the disruption of the blood–brain barrier. **Nag *et al***[2] in this issue of *Lab Invest* demonstrated the upregulation of Ang2 in early phase postinjury, resulting in endothelial cell apoptosis and thus breakdown in blood–brain barrier, followed by upregulation of VEGF-A in addition to the Ang2, leading to a florid angiogenic response. These data are interesting from the therapeutic viewpoint, because anti-Ang2 antibodies and peptide-Fc fusion proteins have recently become available. Anti-Ang2 therapy prevented VEGF-stimulated neovascularization in a rat corneal model of angiogenesis. These results imply that specific Ang2 inhibition may represent an effective antiangiogenic strategy for treating patients with solid tumors. With this view in mind, it would be of interest to analyze the incidence of brain metastasis in trials using humanized anti-VEGF antibody (bevacizumab).

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References

1 Zhu Y, Lee C, Shen F, *et al*. Angiopoietin-2 facilitates vascular endothelial growth factor-induced angiogenesis in the mature mouse brain. Stroke 2005;36:1533–1537.
2 Nag S, Papneja T, Venugopalan R, *et al*. Increased angiopoietin2 expression is associated with endothelial apoptosis and blood brain-barrier breakdown. Lab Invest 2005;85:1189–1198.

Cytokines activate NF-κB in human pancreatic islet cells through CD40 receptor

CD40, a membrane glycoprotein that belongs to tumor necrosis factor receptor family, is naturally expressed on the surface of B lymphocytes and antigen-presenting cells and mediates costimulatory signals for T-lymphocyte activation. The role of CD40 in T-cell activation is well recognized in transplantation and autoimmunity. CD40 signaling is known to activate the NF-κB antiapoptotic transcription factor. In nonimmune cells, however, CD40 receptor signaling has not been fully understood, but reports indicated that it could either induce survival or inhibit growth and enhance apoptosis.

Klein *et al*[1] investigated whether pancreatic islet cells express CD40. They found that isolated human beta cells expressed CD40 and its expression was highly upregulated by incubation of islets with cytokines, which had been known to be associated with autoimmune beta-cell damage. The receptor was functional, which resulted in activation of NF-κB. In this study, they also found that there was a difference in CD40 expression in human and mouse beta cells; CD40 was constitutively expressed in mouse beta cells, but required stimulus in human beta cells, which was the islet isolation process.

These findings suggest that CD40 expression may play a significant role during inflammatory conditions and affect pancreatic islet survival in these conditions.

In this issue, **Hasel *et al***[2] were able to show that in chronic pancreatitis, pancreatic islets had the highest levels of NF-κB with its regulated protein IκBα, survivin, and another apoptosis inhibitor—cIAP1.

Both studies suggest that pancreatic islets elicit properties to evade immune attack, protect themselves against apoptosis and improve their survival in inflammatory conditions.

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References

1 Klein D, Barbe-Tuana F, Pugliese A, *et al*. A functional CD40 receptor is expressed in pancreatic beta cells. Diabetologia 2005;48:268–276.

2 Hasel C, Bhanot UK, Heydrich R, *et al*. Parenchymal regression in chronic pancreatitis spares islets reprogrammed for expression of NFκB and IAPs. Lab Invest 2005;85:1263–1275.