X4 viruses. This discrepancy with the selectivity of jejunal IECs for R5 transcytosis described by Smith and colleagues could be due to several factors. The composition of the viral membrane of HIV-1 generated from HIV-1-infected cells upon contact with IECs could be enriched in adhesion molecules relative to cell-free virus, allowing R5 and X4 virus endo- and transcytosis. Such additional signal might replace the need for a chemokine coreceptor to induce endocytosis. Additionally, cell-free HIV-1 and HIV-1 generated from infected cells could use different internalization pathways. Or, there could be a fundamental difference between the duodenal or jejunal IECs that could affect HIV-1 pathway.

Though further work must be done, Smith and colleagues have added an important piece to the puzzle of the initial step of HIV-1 transmission at mucosal sites. They show that the IECs may act as a selectivity filter for R5 viruses at the time that the individual is initially exposed to the virus. Furthermore, HIV-1 entry at the mucosal site exhibits a peculiar characteristic, irrespective of the structure (monostratified or pluristratified) of the covering epithelium. The first target cell encountered by HIV-1 will necessarily not be infected itself, but may serve as a CD4-independent conveyor to transport the virus to $CD4^+$ cells that would in turn spread the infection. In the case of tight epithelium, IECs would act as a tunnel with a selectivity filter for only R5 viruses, which are mainly responsible for acute HIV infection. This should further understanding of HIV infection, and advance efforts to curtail the infection.

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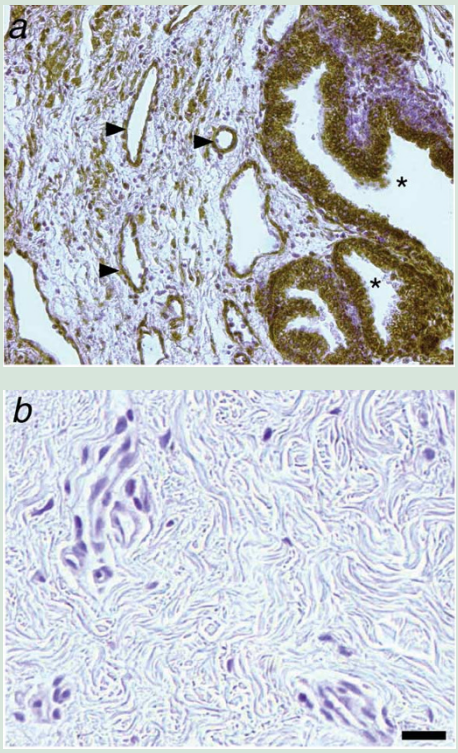
Zip codes: Deciphering vascular addresses



Do circulating peptides contain 'zip codes' that allow them to home specifically to specific vascular beds? If so, one might imagine that discovering these tissue and/or organ-specific peptides might allow for, among other things, tissue-specific targeting of normal blood vessels and of angiogenesis-related targeting of tumor blood vessels. Indeed, Pasqualini and colleagues have shown that such a vascular address system exists in the mouse; a number of peptides that have been shown in mouse models to home specifically to certain blood vessels have been used to deliver cytotoxic drugs and peptides in a tissue-specific fashion. Moreover, coupling drugs to homing peptides, in general, has yielded target compounds that are more effective and less toxic than the parent one.

However, although certain ligands and receptors isolated in mouse models have been used to identify putative human homologs, targeted delivery may not always occur in humans using mouse-derived probes. Indeed, data from the Human Genome Project indicates that the greater complexity of humans derives in part from expression patterns of proteins at different sites and/or levels, rather than a greater number of genes *per se*. Moreover, there have been many examples of species-specific differences in gene expression within the human vascular network.

On pages 121–127, Pasqualini and colleagues now report the first step towards developing a ligand-receptor map of human vasculature—identifying proteins that might be specific to vascular beds within different organs. The authors injected a peptide library containing over 47,000 motifs into a terminally ill patient. They then took tissue samples to identify the distribution of the circulating peptides. They found that the distribution of the peptides is non-random, with some peptides homing to very specific vascular beds and others targeting multiple sites. Moreover, they were able to find certain peptide motifs in circulating ligands that home to specific vascular receptors. For instance, they show by phage overlay on human tissue sections that a prostate-homing page with an IL-11 peptide mimic specifically binds the endothelium of normal prostate (***a***) but not of skin (***b***).

By providing a rudimentary map of the molecular diversity of the vascular system, Pasqualini and colleagues have opened a new avenue to obtain biologically relevant information that could also be used to develop clinical applications. It may now be possible to use this technique to determine the molecular profiles of blood vessels in specific disease conditions, and to exploit this vascular address system to specifically target certain organs and disease states.

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