MILESTONE 15

Con-fusin' co-receptors

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Following the discovery of CD4 as the main receptor for HIV-1 in the mid-1980s (MILESTONE 3), it became clear that expression of a *CD4* transgene rendered human cells, but not mouse cells, permissive for infection with HIV-1. There was also a growing awareness that different HIV-1 isolates have different tropisms in vitro for the infection of different human CD4$^+$ cell types. Macrophage-tropic virus strains (which infect primary macrophages and T cells, but not immortalized T cell lines) predominate during the asymptomatic phase of infection, whereas T cell–tropic strains (which infect primary T cells and T cell lines, but not primary macrophages) become more common during progression to AIDS. The viral envelope protein Env, a ligand for CD4, was known to be the main viral determinant of this cell tropism. Together, these observations led to the suggestion that additional human-specific receptors for Env are required for infection, the expression of which determines cell tropism.

In May 1996, Berger and colleagues identified, in an unbiased manner, the first of these co-receptors for HIV-1. They developed a method to study Env–receptor-mediated cell fusion by expressing a phage T7 polymerase in a CD4$^+$ mouse cell line and a reporter gene linked to the T7 promoter in a second, Env-expressing mouse cell line. Expression of the reporter would occur only in the cytoplasm of fused cells. By screening a cDNA plasmid library from HeLa cells for cofactors that would enable fusion of these nonhuman cells, they cloned a G-protein-coupled receptor of unknown ligand and function, but with the greatest homology to the receptor for the chemokine CXCL8. This cofactor was named 'fusin' in the original paper and was renamed later that year as CXCR4 when its ligand was identified as CXCL12. Importantly, fusin was shown to enable entry mediated by Env from T cell–tropic HIV-1 but not macrophage-tropic HIV-1, which led to a race to identify the second cofactor for macrophage tropism.

That the T cell–tropic factor fusin had homology to an α-chemokine receptor fit well with an observation made the previous year by Cocchi et al. that the β-chemokines RANTES (CCL5), MIP-1α (CCL3) and MIP-1β (CCL4) produced by CD8$^+$ T cells inhibit infection with macrophage-tropic HIV-1. Thus, it seemed likely that a β-chemokine receptor was the cofactor for infection of macrophages.

Five papers published within eight days of each other in June 1996 identified CCR5 as the second co-receptor for HIV-1. Another study by Berger's group, using the same fusion assay that had identified fusin, described the role of CCR5 in macrophage infection. Deng et al. showed that CD4 and CCR5 function cooperatively in mouse cells to permit membrane fusion with macrophage-tropic HIV-1. Similarly, Choe et al. described that macrophage-tropic HIV-1 uses CCR5, as well as CCR3, to facilitate infection. In keeping with the switch in viral tropism that accompanies pathogenesis in vivo, Dragic et al. identified CCR5 as a second co-receptor for macrophage-tropic HIV-1 in primary CD4$^+$ T cells, and Doranz et al. showed that a dual-tropic 'intermediate' HIV-1 isolate used both fusin and CCR5.

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Discovery of CXCR4 and CCR5 as co-receptors provided an explanation for the long-standing puzzle of Env-related differences in HIV-1 tropism and opened up the possibility of developing new antiretroviral drug therapies to block infection. Soon thereafter it was recgonized that individual differences in the expression or activity of these co-receptors could underlie susceptibility to infection and disease progression, and this was confirmed by three papers published later in 1996. Liu et al., Samson et al. and Dean et al. described a 32-base-pair deletion in the coding region of *CCR5* that was variously shown to protect homozygotes from infection, partially protect heterozygotes from infection and delay disease progression in heterozygotes. The lack of an obvious phenotype associated with the mutation, together with the later description of the Berlin patient (MILESTONE 18), gave hope that pharmacological or genetic targeting of CCR5 could be a safe and effective therapeutic approach.

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