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THE V118I MUTATION IN THE REVERSE TRANSCRIPTASE OF HIV-1 DIMINISHES THE INCORPORATION OF MULTIPLE NUCLEOSIDE ANALOGUE INHIBITORS

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M Girouard^{1,2}, K Diallo^{1,2}, B Marchand^{1,2}, S McCormick¹, MA Wainberg^{1,2,3} and M Götte^{1,2,3}

¹McGill University AIDS Centre, Lady Davis Institute-Jewish General Hospital, Montréal, Québec, Canada; ²Department of Microbiology and Immunology, McGill University, Montréal, Québec, Canada; and ³Department of Experimental Medicine, McGill University, Montréal, Québec, Canada

BACKGROUND: HIV-1 resistance to zidovudine and lamivudine has been associated with two different mechanisms. The M184V mutation in the reverse transcriptase (RT) diminishes the incorporation of lamivudine-monophosphate (lamivudine-MP), while zidovudine-resistance conferring mutations were shown to facilitate the phosphorolytic excision of incorporated zidovudine-MP. Previous clinical data have indicated that E44D and V118I amino acid substitutions, when present in a background of zidovudine-mutations, confer dual resistance to zidovudine and lamivudine. The underlying biochemical mechanisms involved in dual resistance to both drugs are unknown. It was the aim of this study to analyse whether 44D and 118I mutations either decrease the incorporation of nucleoside analogue monophosphates or whether these genetic alterations increase efficiency of the excision reaction.

METHODS: We have purified a set of 16 recombinant enzymes that contain E44D and V118I mutations either alone or in a background of different combinations of zidovudine-mutations (41L, 67N, 210W, 215Y). These enzymes were studied in regard to their abilities to accept chain-terminating nucleotides in the context of both of the aforementioned mechanisms.

RESULTS: Mutant enzymes with zidovudine associated mutations at positions 41, 67, 210, 215 facilitate the ATP-dependent excision of zidovudine-MP (two to fourfold), and this effect appears to be moderately increased with the additional presence of the E44D mutation. Unexpectedly, the V118I mutation had no effect on the excision reaction. Conversely, we found that the V118I mutation caused dramatic reductions in rates of

incorporation of zidovudine-MP and lamivudine- MP, respectively. Depending on the mutational background, we determined 10- to 20-fold decreases with respect to the efficiency of zidovudine-mediated chain-termination. The simultaneous presence of the M184V mutation did not significantly compromise these effects. Most importantly, the physiologically relevant phosphorylated forms of abacavir, didanosine, stavudine, zalcitabine, and also tenofovir are likewise incorporated with diminished efficiencies. The V118I mutation alone showed four- to sixfold decreases with respect to the incorporation of chain-terminating nucleotides, while natural dNTP pools are accepted with no significant changes as compared to the wildtype enzyme.

CONCLUSION: Our data make clear that resistance to zidovudine is associated with at least two different mechanisms. A single amino acid substitution (that is, V118I) determines whether decreased rates of nucleotide incorporation or increased rates of excision of the chain-terminator is dominant in this regard. As for the Q151M mutation, the V118I substitution may decrease susceptibility to multiple nucleoside analogues.

PRESENTING AUTHOR: M Götte

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