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A molecular mechanism for WASp and mDia1 collaboration in T cell migration

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In this study, we tested the hypothesis that Wiskott Aldrich Syndrome protein (WASp)-activated Arp2/3 and the mammalian Diaphanous-related formin mDia1 actin assembly activities work in tandem to generate the essential cytoskeletal structures required for T cell chemotaxis. Informed by studies of Drf1$^{-/-}$ mice (mDia1 knockout) generated in our lab, we bred mDia1 knockout with Wasp-targeted animals, postulating that combined mDia1 and WASp ablation would cumulatively impact T cell chemotactic migration. For these experiments, splenic T cell migration in wild-type, Wasp$^{-/-}$, Drf1$^{-/-}$, Wasp$^{-/-}$/Drf1$^{+/-}$ and Drf1$^{-/-}$/ Wasp$^{-/-}$ cells were tested. Wasp$^{-/-}$ T cells were mildly defective in migration when compared to the severe defect again observed in Drf1$^{-/-}$ cells. However, the defect was cumulative in Drf1$^{-/-}$/Wasp$^{-/-}$ T cells; interestingly, the Wasp knockout migratory defect was compounded upon loss of a single Drf1 allele (Drf1$^{+/-}$/ Wasp$^{-/-}$). Further, while Wasp$^{-/-}$ T cell ruffling on adhesive substrates was comparable to that of wild-type cells, Drf1$^{+/-}$/ Wasp$^{-/-}$ T cells failed to ruffle at all. mDia1 and WASp complex in cells. Upon ligation of CD3 and CD28 WASp and mDia1 co-immunoprecipitated and co-localized at the cell periphery within ruffles. Additional experiments identified the shared WASp and mDia1 binding partner DIP/WISH as a linker. In vitro, loss of DIP expression eliminated the WASp-mDia1 complex and blocked T cell migration. Collectively, these data identify a molecular mechanism for collaboration between branching and non-branched actin assembly activities in T cell function.

Biography

Alberts earned BA and PhD degrees from the University of California, San Diego (1983-1993). He was a Post-Doctoral Fellow at the Imperial Cancer Research and the University of California, San Franscisco (1994-1999). In 2000, Alberts joined the Van Andel Research Institute as a Scientific Investigator and Head of the Laboratory of Cell Structure & Signal Integration. He was promoted to Senior Scientific Investigator in 2006 and then to Distinguished Scientific Investigator and Professor of Cancer and Cell Biology in 2009.

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