Vimentin provides the mechanical resilience required for amoeboid migration and protection of the nucleus.

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Dendritic cells employ amoeboid migration through constricted passages to reach the lymph nodes, a crucial homing function for immune responses. Amoeboid migration requires mechanical resilience but the underlying molecular mechanisms remain unknown. As vimentin intermediate filaments (IFs) and microfilaments bidirectionally regulate adhesion-dependent migration, we analyzed whether analogous interactions could be engaged also in amoeboid migration. Vimentin was required for cellular resilience, resulting from a joint interaction between vimentin IFs and F-actin. Reduced actin mobility in the cell cortex of vimentin-reduced cells demonstrated that vimentin promotes subunit exchange and F-actin dynamics. These mechano-dynamic alterations in vimentin-deficient dendritic cells resulted in a striking impairment of amoeboid migration in confined environments in vitro and blocked lymph node homing in vivo in mouse experiments. As nuclear positioning is involved in confined amoeboid migration, vimentin–deficiency resulted in DNA double-strand breaks and cell death in compressed cells. These observations show that vimentin IF-microfilament interactions provide the specific mechano-dynamics required for dendritic cell migration, at the same time protecting the genome against deformation.