Nuclear Rupture at high curvature & high rates causes defects in DNA repair, affecting cell cycle, differentiation, & genome variation

Dennis E. Discher[1]
[1]Molecular & Cell Biophysics Lab, Univ. Pennsylvania, Philadelphia, PA

The nucleus links physically to cytoskeleton, adhesions, and extracellular matrix – all of which are subject to forces. We find nuclear rupture in tumors [1], embryonic organs [2], and various *in vitro* models results from high nuclear curvature and leads to cytoplasmic mis-localization of multiple DNA repair factors and transcription factors. Curvature is imposed by an external probe [1], by migrating quickly (not slowly) through small constricting pores [3,4], or simply by cell attachment to either aligned collagen fibers or stiff matrix [1], and theory indicates rupture pores from by a heterogeneous nucleation mechanism [5]. Mis-localization of nuclear factors is greatly enhanced by depleting lamin-A, requires many hours for nuclear re-entry, and correlates with pan-nucleoplasmic foci of the DNA damage marker γH2AX and with electrophoretic breaks. Excess DNA damage is rescued in ruptured nuclei by co-overexpression of multiple DNA repair factors as well as by soft matrix or inhibition of either actomyosin tension or oxidative stress – with combination treatments needed to rescue cell cycle suppression [4]. Increased contractility has the opposite effect, and stiff tumors with low lamin A indeed exhibit increased nuclear curvature, more frequent nuclear rupture, and excess DNA damage. Normal differentiation processes of myogenesis and ostoegenesis are also affected by migration through constricting pores, suggesting general effects on cell fates [6]. Mis-repair of DNA is further suggested by two cancer lines that, after constricted migration, exhibit greater genome variation [1,3].

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