Title: Nuclear matrix metalloproteases: investigation of novel physiological functions in chicken and frog embryonic neural crest cells.

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Abstract

Neural crest cells (NCC) are exclusively found in all vertebrate embryos. Following formation as epithelial cells at the boundary of neural plate and epidermis, NCC undergo a dramatic epithelial-to-mesenchymal transition and migrate as separated cells from the forming neural tube. NCCs migrate throughout the embryo in a directed manner to differentiate into a variety of cell types, from neurons to skeletal and pigment cells, and to contribute to diverse tissues and organs. Flaws in these processes result in serious birth defects in animals and humans, such as cleft lip and palate, impaired neuronal innervation and aberrant pigmentation.

While the timing and pathways of NCC migration are well characterized, less is known about effectors which promote their separation and motility. Matrix metalloproteases (MMPs) are one such family of effectors. In other contexts, these enzymes are essential to many physiological and pathological processes, including wound healing, implantation and cancer. MMPs mostly act as extracellular enzymes which degrade cell-cell and cell-matrix contacts. Sela-Donenfeld's lab recently found that the gelatinase MMP9 was required in chick NCC to digest the extracellular matrix around the cells and thus allow their migration. Unpublished observation from the Israeli lab in addition demonstrated an unexpected nuclear localization of MMP9 in migratory NCC. Based on this, we hypothesized that MMPs harbor a novel nuclear activity in promoting the motility of embryonic NCCs.

To test this hypothesis, this project' aims were to investigate the nuclear localization and activity of MMPs in NCCs of chick (Sela-Donenfeld) and frog (Blum) embryos, the two best-suited model organisms for investigation of NCC development; to identify the source of nuclear MMPs, namely whether they arise from the cytoplasm or through uptake from the extracellular space; and to determine the role of nuclear MMP in promoting NCC migration. Our results so far confirmed the expression and activity of the two closely-related MMPs, MMP9 (chick) and MMP2 (frog), in migratory NCC. Gain-and-loss-of-function experiments as well as cloning of tagged-MMPs are currently being carried out in the two labs to continue investigating the source and function of these nuclear MMPs. Together, this joint publication will provide initial confirmation to our innovative hypothesis on a new route of control of NCC migration.