doi: http://dx.doi.org/10.7124/bc.0009CF

Lamin A mutations influence Notch signaling and the osteogenic phenotype of human primary mesenchymal cells in a tissue-specific manner

Kseniya Perepelina, Polina Klauzen, Anna Kostareva, Anna Malashicheva

Federal Almazov Medical Research Centre, Saint-Petersburg, Russia
perepelina.kseniya93@gmail.com

Lamin A is involved in many cellular functions due to its ability to bind chromatin and transcription factors and affect their properties. The most known pathological form of lamin - progerin - causes a rare premature aging syndrome or progeria. At the same time, point mutations of the LMNA gene encoding lamin A are more frequent and lead to so-called laminopathies - diseases in which various tissues of mesenchymal origin are damaged. Mutations are often tissue-specific, that is certain mutations lead to the appearance of a single disease phenotype with a muscle, skeletal or adipose tissue being primary involved. How lamins regulate gene expression and cell differentiation remains largely unclear. Mutations R527C and R471C in LMNA are associated with mandibuloacral dysplasia, a congenital disorder characterized by severe alteration of osteogenic differentiation and calcification process. Aim. To explore the influence of LMNA mutations on pro-osteogenic response of human cells of mesenchymal origin and to further explore interaction of LMNA with Notch pathway. Methods. We used lentiviral constructs bearing mutations R527C and R471C and explored its influence on pro-osteogenic phenotype expression and Notch pathway activity in four types of human cells: human umbilical vein endothelial cells (HUVEC), human cardiac mesenchymal cells (HCMC), human aortic smooth muscle cells (HASMC) and human aortic valve interstitial cells (HAVIC). Pro-osteogenic response of the cells was induced by addition of either LPS or specific factors of osteogenic differentiation to the culture medium; phenotype was estimated by expression of osteogenic markers by qPCR; activation of Notch was assessed by expression of Notch-related and Notch-responsive genes by qPCR and by activation of luciferase CSL-reporter construct. Results. Overall, we observed different reactivity of all four cell lineages to the stimulation with either LPS or osteogenic factors. R527C had stronger influence on pro-osteogenic phenotype. We observed inhibiting the action of LMNA R527C on osteogenic differentiation in HCMC in the presence of activated Notch signaling, while LMNA R527C caused activation of osteogenic differentiation in HAVIC in the presence of activated Notch signaling. Conclusion. Our results suggest that the effect of a LMNA mutation is strongly dependent on the cell type and thus is tissue-specific and might be reverse depending on cell type even inside mesenchymal lineages.