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Clusterin enhances migration and invasion of prostate cancer cells through an isoform-specific Akt2/miR-190/PHLPP1 circuit

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During prostate cancer progression cancer cells undergo a variety of molecular alterations that lead to the acquisition of uncontrolled growth properties. One such set of molecular alterations is mediated by the PI3K/Akt signaling pathway. Here, we describe a regulatory system that modulates the phosphoinosited 3-kinase/Akt (PI3K/Akt) pathway downstream of secreted Clusterin (sCLU) in normal and cancer prostate cells. The overexpression of sCLU is very frequent in prostate cancer, and can lead to Akt-activation. This prompted us to investigate how sCLU overexpression influences PI3K/Akt signaling network in a study model represented by human epithelial prostate PNT1A cells stably transfected with sCLU or with empty vector alone. We found that CLU cells show a marked differential phosphorylation of several members of the PI3K/Akt cascade, and in particular of Akt2. Moreover, we found that the phosphatase PHLPP1, known to dephosphorylate Akt2 at S473, is severely downregulated in CLU compared to MOCK cells. We thus investigated whether sCLU alters PHLPP1 protein stability or expression. Our results indicate that sCLU indeed stimulates PHLPP1 degradation by β-TrCP. Interestingly, we further demonstrated that sCLU alters also PHLPP1 through the negative regulator miR-190. Next, because sCLU has been reported to inhibit or to stimulate the aggressive behavior of cancer cells depending on the cell model, we investigated the effects of CLU overexpression or addition of recombinant Clusterin to the medium on cell migration and invasion in PNT1A cell line, which is not expected to display an invasive phenotype, and in the cancer prostate epithelial cell lines LNCaP and PC3. The result was extremely clear: not only CLU overexpression gives PNT1A cells the same behavior of wild-type PC3 cells, but also increases the migration and invasion index of all the above cell models by two to four times, compared to controls. As a confirmation, in the same model silencing of Clusterin abrogates migration of CLU cells. Next, the effect of Akt single-isoform silencing on cell migration was explored. While silencing of Akt1 affected migration only slightly, silencing of Akt2 prevented migration of both MOCK and CLU cells completely. The same result was obtained by pharmacological inhibition of Akt2. All together our results, clearly demonstrate for the first time that Clusterin can switch the low migration phenotype of normal prostate cells towards a high migration phenotype through the modulation of the expression of the PHLPP1 and, in turn, the activity of Akt2.

References

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Keywords

Clusterin, PHLPP1, Prostate cancer, miR-190, Akt