Commentary

Statins as Inhibitors of Lung Cancer Bone Metastasis

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Bone metastases from lung cancer are common events affecting 30–40% advanced lung cancer patients, causing extremely debilitating pain, fracture and spinal compression (Popper, 2016). Cancer cells metastasize to the bone and induce an osteolytic lesion by activating osteoclasts. In addition to conventional treatment of surgery and radiotherapy coupled with pain management, two osteoclast inhibitors, bisphosphonates and the anti-RANKL antibody Denosumab, are currently used for treatment of bone metastasis (D’Antonio et al., 2014). However, these agents have significant side-effects mandating development of safer and efficacious agents to counter bone metastasis.

Statins function by inhibiting HMG-CoA reductase, a rate-limiting enzyme in the mevalonate pathway for cholesterol biosynthesis. Statins are safe and used widely for hypercholesterolemia but their usefulness as anti-cancer drugs are increasingly being appreciated (Demierre et al., 2005). Epidemiological studies clearly demonstrate beneficial effects of long-standing statin use on lowering risk for diverse cancers (Khurana et al., 2007). While statins can directly inhibit proliferation of cancer cells by blocking post-translational modification of RhoA and Ras, recent studies are highlighting their efficacy in preventing bone metastasis from breast, prostate, kidney and lung cancers.

Yang et al. now show that fluvastatin inhibits lung cancer bone metastasis by triggering autophagy in lung cancer cells (Yang et al., 2017). It was documented that fluvastatin inhibits migration and invasion by human lung cancer cells without significantly affecting proliferation and inhibits bone metastasis of these cells when administered by intra-cardiac injection in immunocompromized mice. In a comparative study the inhibitory effect of fluvastatin was greater than that of denosumab. Fluvastatin induces autophagy in lung cancer cells which plays a role in fluvastatin-mediated inhibition of migration and invasion in vitro as well as bone metastasis in vivo as confirmed by using autophagy inhibitors or by Atg5 or Atg7 deletion by CRISPR/Cas9. It was documented that fluvastatin induces p53 which is important for activation of autophagy, and this notion was confirmed by in vitro and in vivo assays using p53 shRNA. Fluvastatin also induces AMPK phosphorylation and mTOR dephosphorylation in a p53-dependent manner without modulating PTEN or AKT pathways. Although several of the findings presented in this paper are already known, the paper provides a comprehensive analysis combining molecular techniques and in vivo imaging (micro-CT) to unravel a potential cascade of events by which fluvastatin prevents lung cancer bone metastasis. The role of autophagy in tumorigenesis and tumor progression is quite complicated causing acceleration of either tumor progression or tumor suppression and is mostly dependent on cancer stages, types and tumor microenvironment. The authors now present an example of autophagy serving a positive role in suppression of bone metastasis.

In bone metastasis, malignant cells release factors, such as IL-6, RANKL, PTHrP and MIP-1α, to stimulate osteoclasts while osteoclasts release IGF-1 and TGF-β to stimulate tumor growth. Statins are known to directly inhibit osteoclastogenesis (Nakashima and Haneji, 2013) and this aspect of statin function has not been addressed in this study. Additionally, immune cells in the microenvironment play a major role in metastasis requiring more stringent analysis of the effect of statins in immunocompetent models. Bone metastasis can also be osteoblastic in nature and the effect of statins on preventing osteoblastic lesions need to be studied as well.

Pilot clinical trial with combination of bisphosphonate (zoledronate) and fluvastatin or atorvastatin in 11 patients with renal cell carcinoma (RCC) could not demonstrate a statistically significant improvement in time to skeletal events (Manoukian et al., 2011). However, there were statistically significant differences in markers of bone resorption indicating that trials with larger cohorts of diverse cancer patients with appropriate controls need to be carried out to demonstrate therapeutic efficacy of this regimen. Preclinical studies with other combinations, such as metformin and simvastatin, have shown promise in prostate cancer bone metastasis (Babcock et al., 2014). These studies depicting efficacy of FDA-approved relatively safe drug combinations show promise for future direction of anti-metastasis therapies.

Conflict of Interest

The author declares no conflicts of interest.

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References

Babcook, M.A., et al., 2014. Synergistic simvastatin and metformin combination chemotherapy for osseous metastatic castration-resistant prostate cancer. Mol. Cancer Ther. 13 (10), 2288–2302.
D’Antonio, C., et al., 2014. Bone and brain metastasis in lung cancer: recent advances in therapeutic strategies. Ther. Adv. Med. Oncol. 6 (3), 101–114.
Demierre, M.F., et al., 2005. Statins and cancer prevention. Nat. Rev. Cancer 5 (12), 930–942.
Khurana, V., et al., 2007. Statins reduce the risk of lung cancers in humans: a large case-control study of US veterans. Chest 131 (5), 1282–1288.

Manoukian, G.E., et al., 2011. Pilot trial of bone-targeted therapy combining zoledronate with fluvastatin or atorvastatin for patients with metastatic renal cell carcinoma. Clin. Genitourin. Cancer. 9 (2), 81–88.
Nakashima, Y., Haneji, T., 2013. Stimulation of osteoclast formation by RANKL requires interferon regulatory factor-4 and is inhibited by simvastatin in a mouse model of bone loss. PLoS One 8 (9), e72033.
Popper, H.H., 2016. Progression and metastasis of lung cancer. Cancer Metastasis Rev. 35 (1), 75–91.
Yang, Z., et al., 2017. Fluvastatin prevents lung adenocarcinoma bone metastasis by triggering autophagy. EBioMedicine 19, 49–59.