Why Older People May Be More Susceptible to Cancer Metastasis

Researchers discover that a molecule that helps cancer cells spread is found at higher levels in otherwise healthy people over 60.

September 3, 2020 By Damon Runyon Cancer Research Foundation

The risk of developing aggressive cancer increases with age as genetic mutations accumulate in our cells from exposure to cancer-causing substances in the environment. Now, former Damon Runyon Fellow John Blenis, PhD, and colleagues at Weill Cornell Medicine have discovered a molecule produced by our own cells that can accumulate in the blood as we age and help cancer cells spread from one site in the body to other organs. The researchers found that the level of methylmalonic acid (MMA)—a by-product of protein and fat digestion—is significantly higher in the blood of otherwise healthy people over the age of 60.

The researchers treated human cancer cells with blood serum samples from people who were either under 30 or over 60. Only the cancer cells treated with serum of older individuals gained the ability to metastasize by detaching from surrounding cells and becoming mobile. When injected into mice, the treated cells quickly migrated to the lungs and started new tumors.

When the researchers analyzed the serum used to treat the cancer cells, they found that MMA was elevated in all the samples that were able to induce metastasis. They then exposed cancer cells to elevated levels of MMA only, and the same transformation was seen.

All the people in this study who had high plasma levels of MMA seemed to be cancer-free, suggesting that the effects of MMA are specific to cancer spread in the body, rather than to initial cancer formation. Cancer initiation and spread are distinct processes that involve different molecular mechanisms.

The researchers also analyzed the genetic changes in the cancer cells and found that higher levels of MMA were associated with increased expression of the SOX4 gene, which contributes to tumor progression and is highly active in aggressive cancers. Blocking the expression of SOX4 stopped MMA from inducing metastasis in mice and drug resistance.

The findings suggest that in the future people could possibly to reduce the protein and fat in their diet to control MMA levels as they age. Alternatively, drugs that reduce MMA levels could be useful in inhibiting metastasis and thus reduce deaths in older cancer patients.

“This discovery is the beginning of investigations in many different directions, but our hope overall is that we’ll be able eventually to develop therapies to reduce MMA levels and thereby reduce cancer mortality,” said Dr. John Blenis.

This research was published in Nature.

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