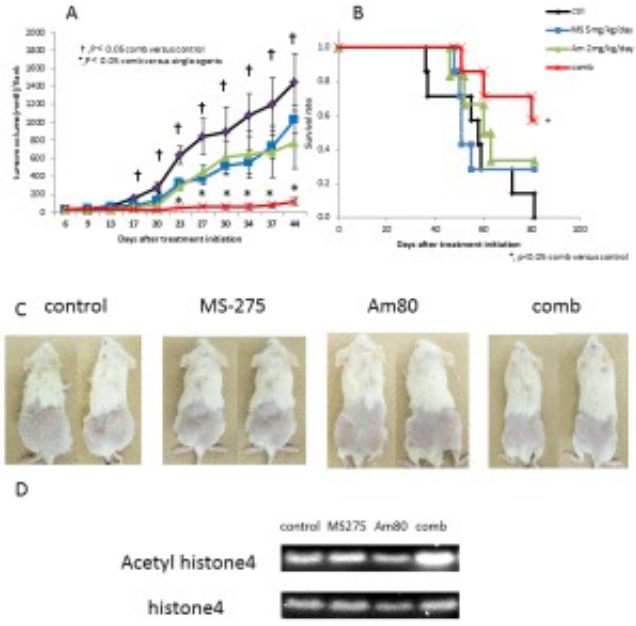
Another prince awakened Sleeping Beauty?

Tumor suppressor genes are one of the body's defenses against uncontrolled growth of tumor cells. When these genes are 'silenced,' or prevented from doing their work, the abnormal cells grow unchecked, usually with fatal consequences to the patient. So, what silences the tumor suppressor gene, and what can be done about it? To understand this complex process, we first need to clarify a number of important, related concepts.



The effect of combination of MS-275 and Am80 on SeAx tumor growth in vivo. Animals bearing an established SeAx tumor were treated with the vehicle, Am80 (2 mg/kg/d), MS-275 (5 mg/kg/d), or a combination of the two agents (A, B). Measurement of tumor volume (A, C). Columns: mean tumor volume; bars: SE; ?: P less than 0.05 versus vehicle control; *: P less than 0.05 versus single agents. Kaplan-Meier survival curves from the treatment groups (B). Statistical significance was measured by using the log-rank test. n = 9, *P less than 0.05 versus control. The experiment was repeated three times with similar results. The western blot of histone 4 acetylation was performed using the samples from the subcutaneously transplanted tumors (D)

The first of these concepts is called DNA methylation. In brief, DNA methylation refers to the addition of a methyl group, a compound made up of hydrogen and carbon atoms, to the DNA. This occurs as part of a so-called 'epigenetic modification,' which is a term used to describe the changes that environmental factors can have on a person's genes. DNA methylation performs a number of vital functions such as properly regulating gene function, or helping embryonic stem cells to develop into specialized cells. However, it can also have potent, damaging effects; it has

been known for close to a decade that it can ‘silence’ a tumor suppressor gene or make it inactive through some kind of process like a metabolic error. Think of it this way: if we liken the tumor suppressor gene to the Sleeping Beauty of the fairytale, the epigenetic modification—in the present case, DNA methylation-- would be the evil spell, and an enzyme called DNA demethylase would be the prince who wakes Sleeping Beauty from her deep slumber—until, that is, we discovered at least one other cast of characters with similar roles.

The new version of our fairytale has a slightly different, expanded cast of characters. The evil spell in this story is now an epigenetic process called histone deacetylation, and retinoic acid receptor (RAR) ?2, a tumor suppressor gene, is the Sleeping Beauty . The prince in this story is called histone deacetylase (HDAC) inhibitor; however, the prince also has a helper, called retinoid, a chemical that has some cancer-fighting properties. We wanted to find out whether combining the retinoid with a HDAC inhibitor could suppress tumor growth in RAR?2-negative human cutaneous T cell lymphoma cells (basically, cancer cells). When we combined the two, we succeeded in restoring the expression of RAR?2, which as you remember, is the name of the Sleeping Beauty in this case, and significantly inhibited tumor cell growth in vitro (artificially), suppressed subcutaneously transplanted tumor growth, and prolonged survival of tumor-bearing mice in vivo (in the experimental animal) more effectively than by either chemical could do alone. In effect, the two chemicals worked together to restore RAR?2 expression even though the DNA methylation of RAR?2 remained unchanged (i.e., the prince who we thought would do something but didn’t). We were able to see proof that our Sleeping Beauty had been successfully awakened in the increased levels of histone H4 acetylation (good gene activity) at lysine 12 and 16 in the promoter region after restoration of RAR?2 expression. This is the first report of histone acetylation as the primary event in the restoration of RAR?2. Inducible RAR?2 expression may serve as a reliable predictor for tumor response in patients undergoing 'epigenetic & differentiation' therapy.

In conclusion, we discovered in our study that there was an alternate Sleeping Beauty story, one that contained a different cast of characters but had the same happy ending—only in this story, the prince had a helper, showing perhaps that reality is rather more complicated than fairytales.

Yukihiko Kato
Department of Dermatology, Tokyo Medical University, Shinjuku, Tokyo, Japan
Department of Dermatology, Tokyo Metropolitan Tama Medical Center, Tokyo, Japan

Publication

Combination of retinoid and histone deacetylase inhibitor produced an anti-tumor effect in cutaneous T-cell lymphoma by restoring tumor suppressor gene, retinoic acid receptor?2, via histone acetylation.
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