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Sanford B H. An alteration in tumor histocompatibility induced by neuraminidase. *Transplantation* 5:1273-9, 1967.
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Enzymatic removal of sialic acid from tumor cells resulted in markedly decreased transplantability in foreign hosts and some decrease in transplantability in syngeneic hosts. It was suggested that antigens at the tumor-cell surface were masked by a sialoglycoprotein at the cell surface. [The SCI® indicates that this paper has been cited in over 215 publications since 1967.]

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During my graduate-student days at Brown University and Roswell Park, I became intrigued with abrupt changes in histocompatibility that tumors occasionally manifested during serial transplantation. Generally these changes involved decreased specificity, with tumors becoming transplantable in foreign strains or sometimes even in foreign species. Such alterations were generally believed to be due to loss of antigenicity as a result of point mutations or gross chromosomal changes, followed by immunoselection of the least antigenic cell types during residence in previously refractory hosts.

One day, not long after completing my PhD thesis with Ted Hauschka and accepting a research position at the Massachusetts General Hospital, it occurred to me that a simple alternative explanation might be the masking of antigens by some substance at the cell surface rather than actual loss. I discussed my idea with a number of senior colleagues. One or two found it intriguing, but in general it was discounted as highly unlikely. This, of course, markedly increased my enthusiasm for exploring this possibility.

One of the tumors available from Hauschka's laboratory was a subline of mouse mammary tumor TA3, which had undergone an abrupt increase in transplantability in foreign hosts and had a histologically and biochemically demonstrable layer of cell-surface sialoglycoprotein. This provided a model, and, to my delight, I was able to show a dramatic increase in resistance to TA3 cells by foreign hosts after removal of sialic acid from the cell surface with the enzyme neuraminidase. In subsequent studies at Massachusetts General, John Codington, Colin Hughes, Roger Jeanloz, and I investigated the mechanisms involved and characterized the sialoglycoprotein.[1-6] Results suggested that cleavage of neuraminosyl groups from the tumor-cell surface glycoprotein exposed an antigenic carbohydrate component and that subsequent clearance of neuraminidase-treated cells incited a particularly effective response to other antigens carried on the tumor cells.

In later work, Simmons at the University of Minnesota[7] and Bekesi and Holland at Mt. Sinai[8] demonstrated a therapeutic effect of neuraminidase treatment in animal models and extended this approach to the clinic. Initial results were encouraging, but expanded clinical studies were disappointing and the approach has since been largely abandoned.

I believe that there are several reasons that this publication has been cited rather frequently. First of all, it ran counter to the thinking of many immunobiologists of that time and excited a certain amount of controversy. Second, two major laboratories initially challenged the results, claiming that tumor cells failed to grow because they were killed by the enzymatic treatment. (Fortunately, we were able to show by a variety of criteria that cells treated as we had described were fully viable, and this objection waned.) A third reason for interest in this paper and its successors was the hope that this approach might lead to a new type of cancer immunotherapy. Although that hope has not been fulfilled, it was rewarding to see the new information that was developed as a result of checking out a rather simple idea that was a bit off the beaten track.

1. **Sanford B H & Codington J F.** Further studies on the effect of neuraminidase on tumor cell transplantability. *Tissue Antigen.* 1:153-61, 1971. (Cited 95 times.)
2. **Hughes R C, Sanford B H & Jeanloz R W.** Regeneration of the surface glycoproteins of a transplantable mouse tumor cell after treatment with neuraminidase. *Proc. Nat. Acad. Sci. US* 69:942-5, 1972. (Cited 90 times.)
3. **Codington J F, Sanford B H & Jeanloz R W.** Glycoprotein coat of the TA3 cell. Isolation and partial characterization of a sialic acid containing glycoprotein fraction. *Biochemistry—USA* 11:2559-64, 1972. (Cited 75 times.)
4. **Hughes R C, Palmer P D & Sanford B H.** Factors involved in the cytotoxicity of normal guinea pig serum for cells of murine tumor TA3 sublines treated with neuraminidase. *J. Immunology* 3:1071-80, 1973. (Cited 25 times.)
5. **Sanford B H, Codington J F, Jeanloz R W & Palmer P D.** Transplantability and antigenicity of two sublines of the TA3 tumor. *J. Immunology* 110:1233-7, 1973. (Cited 60 times.)
6. **Sanford B H.** Neuraminidase and cancer therapy: possible mechanisms of action. *Behring Inst. Mitt.* 55:306-8, 1974. (Cited 5 times.)
7. **Simmons R L, Arantha G V, Gunnarsson A, Grage T B & McKhann C F.** Active specific immunotherapy for advanced melanoma utilizing neuraminidase-treated autochthonous tumor cells. (Terry W D & Windhorst D, eds.) *Immunotherapy of cancer: present status of trials in man.* New York: Raven Press, 1978. p. 123-33.
8. **Bekesi J G, Holland J F, Fleminger R, Yates J & Henderson E S.** Immunotherapeutic efficacy of neuraminidase treated allogeneic myeloblasts in patients with myelocytic leukemia. (Shirigos M A, ed.) *Control of neoplasia by modulation of the immune system.* New York: Raven Press, 1977. p. 573-92.