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Immune surveillance, excerpt from the lecture by Dr. Lawrence Fong, Harnessing the immune system for cancer treatment (2012)
Osher Mini Medical School for the Public University of California Television (UCTV)

So with that, now that we hopefully have some sense of how the immune system works, I’d like to transition to the interaction between cancer and the immune system and introduce two different ideas, on of which is this notion of immune surveillance, the ability of the immune system to basically survey our body and in fact detect and kill cancer cells, and then this whole notion of immune escape, how cancers or tumor cells learn or develop ways to fool the immune system or how the immune system gets tricked to not recognize them.

So in terms of immune surveillance, there’s this immune surveillance hypothesis that was initially proposed by Paul Erlich in the early 1900’s and basically this hypothesis was that the immune system constantly surveys tissues and eliminates tumors before they can become clinically significant. And Paul Erlich was really a medical pioneer in a lot of respects in this notion that the immune system, even though at that time there really wasn’t very much of an idea of what the immune system was. He could postulate this.

And over time pieces of this actually came together to support this hypothesis, including Lewis Thomas, basically showing that tumors can in fact stimulate the immune system and be recognised by the immune system in the 1950’s, and then Frank Burnet proposed this whole notion a couple of years later of evolutionary selection in that the immune system could be recognising tumor and picking it off, but over time, the cancer might change and actually adapt to try to evade the immune system.

And so just to illustrate this whole notion of immune surveillance, we could have a hypothetical tumor, in this case a melanoma cell, and basically these cells can have particular types of proteins that are unique to these cells, in this case, these words here—MAGE, MART, these are called tumor-associated antigens, proteins that are present and are perhaps unique to these melanoma or tumor cells. What happens is that these proteins can in fact be shed by the tumor cells, just because tumor cells, while they grow, they also die, and when they die, they can release proteins.

So these proteins basically get taken up by those antigen-presenting cells that I introduced, those teachers of the immune system, and they would basically go back from the areas of tumor, in this case of skin, back to the lymph nodes where the antigen-presenting cells bearing protein for the melanoma cells would basically educate these CD4-T cells, the helper cells, CD8, or cytotoxic T-cells, by essentially recognising the little bits of protein that are originally derived from the melanoma cell. Then, once these T-cells have been educated, they could actually go back to the tumor site, because the function of these T cells is to protect us from infection or virus, they circulate through our body. They could potentially go back to the tumor and basically recognize this melanoma cell, because they also express these original proteins and target them for destruction.

And so, this is what we believe to happen, in the setting of immune surveillance, and it’s actually a cycle we actually try to tap into in terms of developing immune treatments for cancer.

So what example do we have where this actually happens ?
In fact, if you look at human cancers, there are actually a few different cancers that are associated with immune supression. So, for instance, people who’ve undergone transplantation, whether it’s for a bone marrow transplantation or an organ transplant, like a kidney, those people have to be on immune suppression to prevent their bodies from rejecting the graft. Unfortunately when you suppress a person’s immune system, they’re also susceptible to different types of infections such as Epstein Barr virus. This is a virus that many, of not most of us, harbor, and if your immune system isn’t functioning, this virus basically pops up and can actually cause your immune system to grow and actually develop into tumors.

There are also examples of lymphoblastic lymphomas. This is a cancer of the lymph system as well. Kaposi Sarcoma was a type of cancer that we saw frequently in people who had the HIV infection that progressed to AIDS, so they didn’t have a functional immune system any more. They developed these types of cancers. Cervical cancer, which we know to be mainly caused by human papilloma virus. It’s also more frequent in

individuals with supressed immune systems. And finally stomach cancer, which has an inciting agent, helicobacter pylori, can also be more frequent in people who are immune suppressed.

There is a complication in these different types of cancers in that these types of cancer are associated with different types of infection. But the important part is while these viruses tend to be present in a lot of people, these tumors develop much more frequently in people whose immune systems are not functioning.

Now if you sort of look at the flip side, and look at different types of cancer, and see how people do with those cancers, what we found is that people who have lymphocytes within certain types of tumors such as breast, esophageal, prostate, melanoma, renal cell, ovarian, colorectal cancer. If those lymphocytes are there, those are actually associated with a better outcome, suggesting that the immune system is actually doing something favorable, or is indicating something favorable with regards to these different types of cancers.

So I'm just going to give a couple of examples of this. This is an example of ovarian cancer. This was actually published in the New England Journal. So this is not a fringe science, this is something that is actually very high visibility and that people are thinking about.

What these curves are, and I'll be showing a few of these curves as we go, they're called Kaplan Meyer plots, and what they are, on the X axis, so the horizontal axis, is basically time, months, so how long is a person doing OK, or how long is a person living. On the Y axis are different things, in this case, this is called progression-free survival, so how long does a person live before their cancer gets worse or comes back. And in this case, it's overall survival. How long does a person actually live. The main point I want to raise here is if you look at women who have ovarian cancer and you actually look in their abdomen, where their tumors are, there's often fluid that's there, if a woman has T cells within their tumor and their fluid, they actually survive a lot longer than women who have no T cells or no immune response going on within their tumors. And that's true whether or not you look at patients who undergo surgery –what this panel illustrates on the bottom. You look at patients undergoing chemotherapy. The results are pretty striking, you can see these red curves, those women who have immune responses or these T cells within the tumor, so actually significantly better.