EXPANDING THE RESEARCH HORIZON

In Ankylosing Spondylitis – Understanding the Role of HLA-B27

By Robert A. Colbert, MD, PhD

Most patients with ankylosing spondylitis (AS) recognize HLA-B27 as a genetic marker that they carry. Indeed, it is found in the vast majority (90-95%) of patients with this disease, compared to less than one of ten healthy people. It is inherited from one parent, and in rare cases both, and is often accompanied by the knowledge that someone else in the extended family has AS or another HLA-B27-associated disease.

We also know that HLA-B27 does not work alone. Several additional genes contribute to AS, and major efforts in North America and around the world are dedicated to finding the location of these genes in the human genome. What is often less well appreciated is that HLA-B27 is already a major focus of research, and understanding its role in disease will provide a key piece to this puzzle. Since the discovery of the HLA-B27 – AS connection over 30 years ago, we have learned a great deal about what HLA-B27 does; unfortunately, this has not answered the question of how it causes disease. Recently, new research has uncovered some very unusual features of HLA-B27, and the paradigm has begun to shift toward the idea that an abnormal property of HLA-B27 may be the basis for its connection with disease.

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HLA-B27 – a carrier of peptides

What does HLA-B27 do? The product of the HLA-B27 gene is a member of a family of proteins called human leukocyte antigens (HLA) that have an important role in the immune system. T cells are a type of white blood cell that recognize HLA-B27 and decide whether to react to it or ignore it, depending on its shape or surface contour, which in turn depends on the type of peptide it carries. Peptides are small bits of proteins that are produced when the proteins are broken down. The peptides can come either from proteins that our own body makes (self-peptides), or from microbes like viruses or bacteria (foreign peptides). Normally T cells ignore self-peptides and react to foreign peptides, producing chemicals called cytokines that cause an inflammatory reaction. The ability of T cells to recognize and react to foreign peptides carried by HLA proteins is one means that our immune system uses to fight off infections. We know that HLA-B27 works as well as, or perhaps even better than other HLA proteins in helping to fight off viral infections. For example, people with HLA-B27 who have become infected with HIV tend to stay healthy longer than others, and also infection with the hepatitis C virus tends to be cleared more completely. Why this occurs is not known.

For a long time it was thought that people with HLA-B27 developed AS because their T cells were fooled into thinking that the self-peptides carried by HLA-B27 were really foreign peptides. Despite how attractive this idea is, it has been very difficult to find T cells that react against HLA-B27 and its self-peptides (autoreactive T cells). Furthermore, in animal models where HLA-B27 causes an inflammatory disease like AS, there is solid evidence that this idea is not correct.

HLA-B27 – a protein that misfolds

If the peptides carried by HLA-B27 do not cause AS, what does? Several years ago scientists began to look for another explanation. Examining HLA-B27 from a different perspective, they discovered that in addition to its normal activity of carrying peptides, it also has at least two abnormal properties. One is a tendency for the pro-

tein to 'misfold' and the second is that it can form an unusual structure called a 'dimer' where two HLA-B27 proteins are attached to one another. Both of these findings suggested alternatives to the notion that the peptides were the key to understanding the role of HLA-B27 in AS.

What is protein misfolding? One of the most striking examples of protein misfolding is what happens when you boil an egg. Proteins in the egg 'white' and yolk become irreversibly denatured or misfolded, to the point where the process can never be reversed. (Ever try to unboil an egg?) Over the last several years there has been increasing recognition that a number of genetic diseases result from protein misfolding. However, the symptoms of the disease, and the abnormal processes that cause these symptoms, can be quite varied and depend on many factors. For example, proteins that misfold just after being made are often broken down very quickly, and as a result the protein is missing and not available to do its job. This is known to occur in certain types of hemophilia (bleeding disorder). When misfolded proteins are not eliminated quickly and build up in tissues outside the cell, they can also wreak havoc by preventing other cells from carrying out their function or even to die. This is important in certain neurological diseases including Alzheimer's.

HLA-B27 misfolding and the unfolded protein response. We are just beginning to learn more about the implications of HLA-B27 misfolding. First, since protein misfolding can be a little complicated, it's worth a more complete explanation. The story begins inside the cell, in a compartment known as the endoplasmic reticulum (ER). HLA-B27 is made here, and stops long enough to pick up its peptide cargo before delivering it to the cell surface. In order to carry this

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cargo, it needs to fold into a certain shape that allows the peptide to fit. It seems that this is where the problem is – HLA-B27 doesn't get into shape very well.

There are a lot of other proteins that try to help, but if there aren't enough or they aren't working well, HLA-B27 tends to accumulate. This is a particular problem when the cell is trying to make a lot of HLA-B27 such as during an infection or an immune response. These incompletely folded (and/or misfolded) HLA-B27 proteins can cause ER 'stress'. This in turn activates a series of complex events that result in an 'unfolded protein response' (UPR). The UPR increases the assembly line machinery responsible for folding and secreting proteins, and also the capacity to break down proteins that have misfolded, and is one way that the cell adapts to ER stress.

A surprising finding has been that the UPR seems to have additional effects in immune cells. When the UPR is activated, certain immune cells 'over-respond' to products that come from bacteria and viruses. Some of the overproduced cytokines not only promote inflammation, but are also linked to increased bone formation. This could be important in AS, since another aspect of this disease that is not understood is the tendency to form too much bone in certain places and too little bone in others. There are many studies underway to better define how HLA-B27 misfolding may be important in the development of AS.

Abnormal forms of HLA-B27. In addition to misfolding, the formation of HLA-B27 dimers on the cell surface also has possible implications. We have learned that 'natural killer' or NK cells, in addition to T cells, can recognize HLA proteins. NK cells use a different type of 'receptor' that may be able to selectively recognize HLA-B27 dimers in addition to the traditional forms on the cell surface. NK cells are one of the first lines of defense used by the immune system, and if recognition of the abnormal HLA-B27 dimers changes their function, this could contribute to a chronic inflammatory disease.

Summary

As we gained a more complete knowledge of what HLA-B27 does during the 1980s and 1990s, there was a strong sense that we were only a few years from understanding its role in AS. This was bolstered by the development of animal models where HLA-B27 and the immune system could be manipulated to test various ideas and perhaps even be used to discover better treatments. Although these goals have not yet been realized, there is a renewed optimism that this puzzle can be solved. The discovery of additional genes that contribute to AS will be important as the function of their gene products should inform us on the role of HLA-B27, and may identify additional approaches to treat the disease. Ultimately, these efforts are aimed at finding better ways to treat AS, and perhaps even think about a cure.