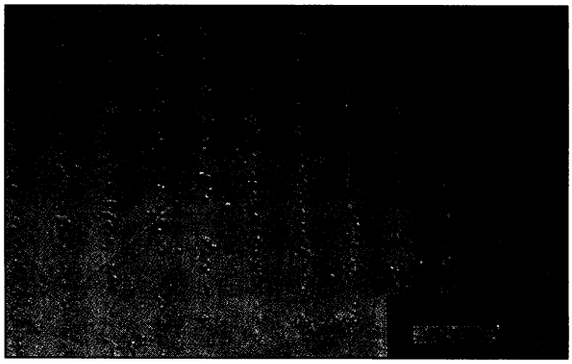
hydroxyl groups then act as links to which the researchers attach peptide sequences—known as YIGSR sequences—from laminin.

In the December issue of the *International Journal of Developmental Neuroscience*, the researchers reported that when they placed mouse nerve cells on their scaffold, the cells bound selectively to regions with the YIGSR-modified Teflon. Moreover, when new neurite branches grew from these cells, they followed the patterned surface. "This is a critical demonstration that you can pattern polymers and nerves will follow the patterns," says MIT's Christine Schmidt, who is researching directed nerve-cell growth. Now the researchers are working to roll their modified fabrics into tubes that can be wrapped around damaged nerves in the body.

Designer liners

Teflon has a long history as another type of implant: artificial blood vessels. But here its history is somewhat spotty. Although the synthetic works well on large-diameter vessels—wider than 6 mm—smaller vessels develop problems. These vessels typically clog up within 2 years after implantation—platelets and smooth muscle cells in the blood begin sticking to the surface of the polymer mesh, occluding the opening. This wouldn't happen if the implant walls more closely resembled natural blood vessels, so scientists are re-engineering them to do just that.



Nerves grown in a row. *(Top)* By attaching cell adhesion molecules in patterns on a Teflon sheet, researchers have been able to bind nerve cells to the sheet (scale bar = 100 microns). Growing neurites from these cells *(right)* follow these patterns.

"We're trying to take surfaces that are recognized [by the body] as foreign and change them into something the body really likes," says BSI's Clapper. What the body likes in the case of blood vessel inner walls are endothelial cells, which normally create a slippery surface on those walls that prevents platelets and smooth muscle cells from adhering. The strategy Clapper and several other researchers are pursuing is to induce those cells to bind to the inner walls of polymer vessels.

Researchers have long known that extracellular matrix proteins such as fibronectin and laminin promote endothelial cell binding to different surfaces. Since the early 1980s researchers have identified a number of different peptide sequences of these proteins that are responsible for the adhesion. One, the REDV sequence, was singled out in 1986 by Martin Humphries and Kenneth Yamada at the National Institutes of Health in Bethesda, Maryland. And in 1991 Jeffrey Hubbell, a chemical engineer at the California Institute of Technology in Pasadena, showed that in vitro, the sequence enhances endothelial cell binding to the common graft polymers PTFE and polyethyleneterephthalate.

At the same time work has also progressed with polymers modified with other peptides. In the July issue of the journal *Heart Valve Disease*, researchers report the first in vivo results on a polymer coated with the RGD sequence, made up of arginine, glycine, and aspartic acid. Catherine Tweden and her colleagues at St. Jude Medical, an implant company in St. Paul, Minnesota, along with William Craig and collaborators at Integra Life Sciences in La Jolla, California, report that they implanted RGD-coated polymer patches in the aortas of dogs. After 33 weeks, endothelial cells covered 75% of the RGD coated patches, three times more area than was covered in controls without the peptide coating. The Integra researchers are now implanting RGD-coated synthetic vessels into animals to see if grafts show the same benefit.

The blood vessels, researchers hope, are harbingers of implants to come. Implant researchers are modifying surfaces of a host of other devices, including those for hip joints and breast and dental implants. But like the research on assembling cells into complex tissues, this work remains in its earliest stages. Most of the promising results come from lab studies of how cells interact with hybrid scaffolds. In large part, it remains to be seen how such materials will behave in the bodies of animals, let alone humans. And before that final step can be taken, researchers must convince health officials that any implanted material and its byproducts are safe. Says Rutger's Yarmush, "a lot of detailed work needs to be done."

–Robert F. Service

IMMUNOLOGY

How the Glucocorticoids Suppress Immunity

If you are diagnosed with a disorder caused by an overactive immune system, such as an allergic skin reaction or a serious inflammatory disease like rheumatoid arthritis, chances are your physician will prescribe one of a class of steroid drugs called glucocorticoids. But ask how these drugs suppress immune reactions, and you are likely to get a shrug. Even though they have been mainstays of clinical immunology for decades, researchers have had few clues about how the glucocorticoids suppress immune and inflammatory reactions—until now, that is.

Work described on pages 283 and 286 by two research teams, one led by Albert Baldwin of the University of North Carolina, Chapel Hill, and the other by Michael Karin of the University of California, San Diego, points to what could be a major immunosuppressive mechanism of the drugs. Researchers have known for several years that the drugs, which are derivatives of hormones whose effects include helping the body respond to stress, work by interfering with immune cells' ability to turn on many of the genes needed to mount effective immune responses. The new work suggests that a large part of this effect occurs because the drugs stimulate production of a protein called IκBα, which locks up a key activator of the genes known as NF-κB, so that it can't do its job. "We understood [the glucocorticoids'] end effects, but we didn't understand the path through which they work," says immunologist Jeffrey Leiden of the University of Chicago School of Medicine. These papers, he adds, provide "a simple and elegant explanation of at least one pathway."

The explanation they offer may do more than satisfy immunologists' curiosity about how the glucocorticoids suppress the immune system. Many of the conditions for which they are prescribed require long-term treatment, and that can lead to undesirable side effects, such as cataracts, weakened bones, and abnormal fat accumulation. "The glucocorticoids are a really fantastic development for treating many human diseases. The problem is the side effects," says Anthony Cerami of the Picower Institute in Manhasset, New York, whose team is also studying the drugs' mechanism of action. But if they do indeed work by inhibiting NF-κB activity, chemists might be able to design

new immunosuppressive drugs that do the same job with fewer side effects.

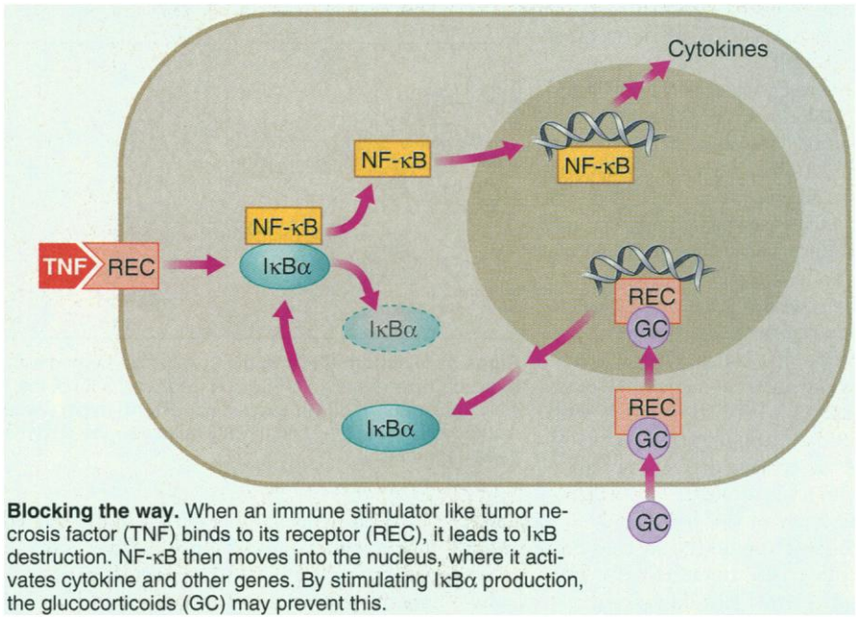
The glucocorticoid drugs and hormones haven't been an entirely closed book. They regulate many other genes besides those needed for immune responses, and researchers have developed a clear picture of how they perform this function. When the drugs or hormones enter the cell, they bind to a receptor in the cytoplasm and form a complex that moves into the nucleus, where it acts as a transcription factor that turns genes either on or off. Among the genes turned on, for example, are those involved in stress reactions, such as the genes that make the enzymes needed to produce the sugar glucose, which gives cells a quick energy boost.

But many of the immune-system genes turned down by the glucocorticoids appear to lack a necessary feature for that regulation. These include genes encoding cytokines such as the interferons and interleukins, which activate immune cells, as well as those for cell adhesion molecules that draw immune cells into inflammatory sites. And very few of those genes carry the DNA sequence the glucocorticoid-receptor complex binds to when it regulates genes. That suggested the complex works indirectly. But how?

Researchers thought they had a clue 5 years ago, when several teams, including Karin's, found that glucocorticoids prevent another transcription factor, AP-1, from binding to its target genes and turning them on. Among the genes so inhibited, Karin and his colleagues found, is the one for the protein-dissolving enzyme collagenase, which is a major contributor to the tissue damage of inflammation. Indeed, Karin describes collagenase as "the number-one enzyme for destruction of connective tissue in rheumatoid arthritis patients." Despite that, he says that not all of the glucocorticoids' immune effects are likely to be explained by blocking AP-1 activity. For one thing, most of the steroids' potential target genes lack AP-1 binding sites, just as they lack binding sites for the glucocorticoid-receptor complex.

What they do have binding sites for, however, is still another transcription factor—NF-κB, which in the past several years has emerged as a regulator of many cytokine and cell adhesion genes. That discovery prompted researchers, including Karin and Baldwin, to see if glucocorticoids might somehow interfere with NF-κB activity. About a year ago, four research teams, Baldwin's among them, got the first inkling that they might do so: They showed that the glucocorticoid receptor complex binds to NF-κB and prevents it from binding to DNA and increasing gene activity. While that presented another possible mechanism by which the glucocorticoids might suppress the immune system, Baldwin says that other observations made during the course of those experiments suggested that direct binding of the complex to NF-κB was not the only, and perhaps not even the major, way the glucocorticoids were working.

In unstimulated immune cells, NF-κB is held in the cytoplasm in complexes with another protein, either IκBα or the structurally related protein IκBβ. Stimulation of the cells by any of a variety of immune signals results in the addition of phosphate groups to the IκBs, a chemical change that triggers their breakdown and releases NF-κB. The NF-κB then migrates to the nucleus, where it activates its target genes. But the researchers found, Baldwin says, "that in the presence of glucocorticoids the amount of NF-κB that went into the nucleus was significantly diminished," while IκBα concentrations were higher than expected. This suggested that the glucocorticoids were working through IκBα.



Blocking the way. When an immune stimulator like tumor necrosis factor (TNF) binds to its receptor (REC), it leads to IκB destruction. NF-κB then moves into the nucleus, where it activates cytokine and other genes. By stimulating IκBα production, the glucocorticoids (GC) may prevent this.

Meanwhile, Karin and his colleagues were coming to a similar conclusion. They showed that the glucocorticoid dexamethasone inhibits activation of the interleukin-2 gene by both AP-1 and NF-κB—but that only the NF-κB effect requires new protein synthesis. This result suggested that the glucocorticoid stimulates production of another protein that inhibits NF-κB action, and the likely candidate was an IκB. And that's what both groups have now shown directly.

They've found that glucocorticoids increase transcription of the IκBα gene into RNA, the first step of protein synthesis. As a result, IκBα concentrations go up within the cell, allowing the protein to hold NF-κB in inactive form in the cytoplasm even under conditions when it would normally be released to move into the nucleus.

And the effect is not just limited to cultured cells, as Karin's team showed that it also occurs in mice. "As far as I can tell," says Karin, the increased production of IκBα and consequent block in NF-κB activity "can explain the major effects of glucocorticoid, which is shutting off cytokine production." Indeed, agrees Baldwin, "by inhibiting NF-κB, you can really knock the legs out of an immune response." The North Carolina worker suggests, however, that direct binding of the glucocorticoid-receptor complex to NF-κB may still play a role in the immunosuppression. Should any of the transcription factor escape from IκBα, the complex could bind NF-κB in the nucleus and prevent it from reaching the DNA.

But however NF-κB's activity is blocked, its inhibition is turning out to be an important mechanism of action for anti-inflammatory drugs generally. Last year Sankar Ghosh, a Howard Hughes Medical Institute investigator at Yale University School of Medicine, and his colleagues obtained results suggesting that aspirin, a nonsteroidal anti-inflammatory drug, exerts some of its effects by inhibiting NF-κB activity, although only at very high concentrations (*Science*, 12 August 1994, p. 956).

And the central role of NF-κB inhibition in suppressing immunity could point the way to improved immunosuppressant and anti-inflammatory drugs. "Once you know the mechanism, you can begin to set up rational screens for other [NF-κB] inhibitors," says Leiden. "What you are looking for is a better safety–side effect profile." Whether such drugs can in fact be found remains to be seen. But researchers are already encouraged by what they are learning about glucocorticoid action. "I think the findings are very significant," says Ghosh. "This just makes sense in many ways."

–Jean Marx