Volume 83 • Number 7 • July 2003

INSIDE LAB INVEST

CLAUDIN-4 EXPRESSION PEYER'S PATCHES: Gut-associated lymphoreticular tissue (GALT) mediates the priming of Th1/Th2 lymphocytes and IgA-committed B cells in response to antigens passing the mucosal barrier of the intestine. The morphologic entity associated with this activity is the Peyer's patch, a unique structure that not only contains the cellular machinery needed to activate immune responses, including professional antigen-presenting cells (APCs) such as macrophages and dendritic cells, lymphocytes, and a supporting stroma. These patches also contain a unique covering called the follicle-associated epithelium (FAE). Although the role of the FAE remains incompletely understood, it is known to be populated by M cells. These cells are involved with the sampling of orally encountered antigens and their delivery to underlying APC cells, and one recent report suggests that these cells may even mediate HIV entry through the mucosal barrier. A central question has thus been the route by which luminal antigens traverse the FAE en route to the APCs, and whether the FAE differs in any other way from the epithelium that covers the rest of the intestinal villus. In this issue, **Tamagawa and colleagues** focus on one aspect of this problem by examining the distribution of claudin expression in the FAE (Lab Invest 2003, 83: 1045–1053). The claudins are a superfamily of over 20 related membrane proteins that form the fibrillar strands of the tight-junction of epithelial cells. Earlier studies have established that there is wide variation in the claudin composition of tight-junctions from different tissues and even from different regions within the same tissue. Thus, whereas in the liver claudin-2 is expressed as a gradient increasing from the pericentral to the portal region, claudin-3 is uniformly expressed, and claudin-4 is absent. In the intestine, there is a reduction in claudin-2 as one moves toward the villus tip, and highly restricted expression of claudin-4 at the villus tip and in the FAE. The importance of these studies derives from observations that tight junctional paracellular permeability is in part determined by the claudin composition. Thus, the finding that a unique form of claudin is present in the FAE may offer a molecular insight into one mechanism controlling antigen access to the underlying GALT. As described in Tamagawa's report, there also seems to be an association of claudin-4 with apoptosis of the adjacent epithelium. The significance of this remains unclear. In future studies, it will be of interest to see if the targeted deletion of claudin-4 alters mucosal immunity or the selectively of the mucosal barrier to orally acquired antigens.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS AND ANTI-ANGIOGENESIS—OLD TREATMENTS AND NEW USES: Since its discovery over 100 years ago, aspirin (a cyclooxygenase inhibitor) has been heralded as a wonder drug, being used to alleviate symptoms in a myriad of conditions ranging from headache to thrombosis. Since their discovery, other cyclooxygenase inhibitors including indomethacin and more recently the COX-2 inhibitors have been developed. These nonsteroidal anti-inflammatory drugs (NSAIDs) have been routinely used as effective anti-inflammatory and analgesic drugs in a variety of diseases. The latest generation cyclooxygenase inhibitors—specific cyclooxygenase-2 (COX-2) inhibitors—are currently widely prescribed as anti-arthritic drugs. Following their introduction as therapeutic agents, it was recently discovered that, in addition to their expected therapeutic effects, NSAIDs can affect the incidence and progression of certain human cancers. Experiments performed using COX-2 deficient mice provided confirmatory evidence as to the potential importance of modulating this enzyme in cancer patients. To date, in spite of their growing acceptance as effective anticancer agents, the underlying mechanism(s) of their actions remains incompletely understood. In this issue, **Yoshida et al** present evidence supporting the concept that COX-2 activity plays a role in tumor-induced angiogenesis (Lab Invest 2003, 83: 927–938). Using a murine sponge implant model, these investigators have previously demonstrated an increase in VEGF expression following addition of exogenous COX-2 or exogenous prostaglandins and inhibition of this COX-2 induced angiogenesis with administration of antisense oligonucleotides specific for VEGF mRNA. In this report they identify the COX isoforms that mediate angiogenesis and characterize the downstream molecules responsible for this phenomenon. These studies illustrate the importance of the COX-2/VEGF pathway as a dynamic modulator of both tumor-induced and reactive (reparative) angiogenesis, and serve as an illustration of the general nature of this angiogenesis inhibition and the widespread, varied effects such treatments are likely to have on diverse patient populations.

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THE MANY ROLES HIDDEN IN A NAME: When a new molecule is discovered, usually in the process of investigating a normal or pathological function, it receives a name related to its physiological role, a function-related name. This is all well, but in the vast majority of cases, alternative functions are discovered by later investigations, and occasionally it is realized that the original discovery did not concern the major biological function. If the extension of the physiological role comes a significant time after the christening, the name sticks, no matter how inappropriate it is. The fact is that most proteins multi-task; thus, it is not surprising to read in this issue of the journal that relaxin is no exception. **Samuel et al** present a study of the role of relaxin in murine male development using the gene knockout approach to probe function (Lab Invest 2003, 83: 1055–1067). The protein that facilitates female reproductive function turns to interfere with male fertility by causing sperm immaturity and a significant increase in the rate of cell apoptosis in the testis and prostate. The descriptive data suggest that relaxin may mediate its effects in the male by anti-apoptotic activity—one more action not suggested by its name related to the act of delivering one's progeny!

THE LIFE AND DEATH OF HEPATOCELLULAR CARCINOMAS: Failure of apoptotic cell death is considered important in hepatocarcinogenesis because of the inherently high proliferative potential of hepatocytes during liver regeneration. Human hepatocellular carcinomas indeed show resistance to apoptosis mediated by several known "death" receptors. A number of anti-apoptotic mechanisms, such as reduced expression of Fas, caspases, and increased expression of the anti-apoptotic Bcl-2 and IAP families contribute to the resistance of human hepatocellular carcinomas to immune-mediated cytotoxicity. In this issue, **Okano et al** identify cFLIP (cellular FLICE/caspase-8 activation protein) to be constitutively expressed in all human hepatocellular cell lines examined (Lab Invest 2003, 83: 1033–1043). cFLIP inhibits apoptotic signaling pathways mediated by all known death receptors, including Fas, TNF-R, and TRAIL. These data suggest that resistance to apoptosis in hepatocellular carcinomas is likely because of the intracellular action of cFLIP rather than to alteration of "death receptor" expression or an increase in the expression of "decoy" receptors. cFLIP also may contribute globally to hepatocellular carcinoma by activating known survival pathway involving NF-κB.

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