regulatory T cells in the settings of autoimmune disease, allergy, and tissue or organ transplantation. Although many questions remain to be answered, direct targeting of immature DCs, as described by Mahnke and colleagues, offers an exciting new therapeutic opportunity for their induction in vivo.

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Gene expression profiling illuminates myeloma biology

An abiding mystery in multiple myeloma (MM) has been the surprising heterogeneity in clinical outcome that characterizes this morphologically homogenous disease. For example, survival may be influenced by the immunoglobulin isotype expressed by MM cells. Similarly, some patients develop bone disease while others are spared. The genetic basis for both observations is obscure. Now, pioneering gene expression profiling studies are addressing such unexplained clinical truisms through the development of a comprehensive molecular portrait of the disease (Claudio et al, Blood. 2002;100:2175-2186; and references below).

A common theme of these early studies is the realization that MM can be classified into subgroups that associate with a normal physiologic counterpart of plasma-cell differentiation (Zhan et al, Blood. 2003;101:1128-1140; Tarte et al. Blood. 2002;100:1113-1122). In brief, some MM cells resemble late-stage B cells while others associate genetically with their normal, fully differentiated plasma cell counterparts. The proliferative nature of “B cell–like” MM seems evident from the expression profile and the clustering of such MMs with end-stage human MM cell lines (Zhan et al). Nevertheless, clinical evidence of poor outcome associated with a B cell–like profile is, as yet, lacking.

In this issue, Magrangeas and colleagues (page 4998) have taken such observations one step further. The gene expression profiles of 92 newly diagnosed patients are reported. Two clinically relevant observations result. First, expression profiles reveal a unique molecular signature that distinguishes IgA from IgG, or light-chain, disease. In a second clinically relevant finding, several genes discriminate between κ and λ MM. Remarkably, a strong association was noted between a κ subgroup expressing high levels of Mip-1α and active myeloma bone disease. Thus the transcriptional profiles of a plasma cell and its growth-arrested MM counterpart appear linked, relate to the stage of development of the cell, and reflect various differentiation processes, including isotype switching. By inference, these unique MM expression profiles linked to plasma-cell differentiation may explain previously noted clinical observations.

These studies are among the first to link molecular profile to clinical observation in this disease and support the hypothesis that a differentiated hierarchy of plasma cells exists in MM. Apparently the stage of growth arrest in MM correlates with and may, in part, explain clinical phenotype. Further studies of clinical outcome and its relationship to expression profiles are required to further this hypothesis.

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Cryptic malaria parasites unveiled

Until a few years ago the dogma was that mature erythrocytic stages of Plasmodium falciparum adhered to host endothelial cells but that earlier “ring” forms were not able to bind and so were seen in the peripheral circulation. This disappearing act of the parasite has been linked to severe disease. But the recent demonstration that ring forms of the parasite are able to cytoadhere (Pouvelle et al, Nat Med. 2000;6:1264-1268), confirming pathologic observations, raised the specter of completely cryptic blood-stage populations of parasites in humans.

From this earlier work it was clear that the molecule(s) responsible for ring-stage cytoadherence were not the same as that involved in binding of later stages, namely PfEMP1, which raised the question: what might be the parasite ligand for this interaction? In this issue, Douki and colleagues (page 5025) have extended their previous work, identifying the smaller of 2 molecules implicated in adhesion (RSP2) as a rhoptry-derived protein, RAP2. In doing so, they provide an explanation as to how newly infected erythrocytes are able to cytoadhere directly after invasion and have also provided a mechanism to explain the curious phenomenon of uninfected erythrocyte sequestration during malaria infection. Insertion of RSP2/RAP2 into seemingly uninfected erythrocytes may have a role in the development of malarial anemia, one of several clinical forms of severe malaria.

A number of important questions remain, particularly what is the basis of the association of ring-stage adhesion with chondroitin sulfate A (CSA) binding, often seen in placental malaria (Scherf et al, Cell Microbiol. 2001;3:125-131). The possibilities include the physical proximity in the P falciparum genome of RSP2/RAP2 and the subtelomeric region, containing genes that encode PfEMP1, and specific forms of RSP2/RAP2 in CSA-binding parasites. Further work will be needed to unravel the molecular mechanisms involved in ring-stage adhesion, but the results published in this issue make a significant contribution to efforts to decode the language of malaria parasite adhesion.

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Diamond-Blackfan anemia and nucleolar transport

Diamond-Blackfan anemia (DBA) is a rare congenital hypoplastic anemia characterized by pure red blood cell aplasia and congenital abnormalities. Curiously, 25% of individuals with DBA carry one mutant allele of the RPS19 gene. RPS19 is a protein subunit of the ribosome, and ribosomes are assembled in the nucleus, more specifically in the nucleolus, of eukaryotic cells. How RPS19 deficiency affects ribosome assembly or results in the developmental defects of DBA remains unknown.