GENETIC PREDISPOSITION FOR THE DEVELOPMENT OF ONJ

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In this issue of Blood, Sarasquete and colleagues report that the rs1934951 polymorphism mapped within the cytochrome P450-2C polypeptide 8 gene (CYP2C8) is associated with increased risk for the development of ONJ in myeloma patients who receive intravenous BPs.

Osteonecrosis of the jaw (ONJ) is a potentially serious complication of bisphosphonate therapy (BPs), characterized by the development of exposed bone in the oral cavity with no healing of the soft tissue for more than 8 weeks of follow-up. Pathologically, the lesions are characterized by necrotic and acellular bone associated with a quiescent bone surface. The cause of ONJ in myeloma is uncertain and likely multifactorial. The incidence of ONJ is higher after the use of the more potent intravenous BPs and when invasive dental procedures are performed. The risk for ONJ increases with BP treatment duration and has been reported to be 5% to 15% at 4 years. Guidelines for the prevention, diagnosis, and management of ONJ have been proposed by both the American Society for Clinical Oncology and the Mayo Clinic. It seems that appropriate preventive measures, such as a detailed assessment of dental status by experienced specialists and avoidance of invasive dental procedures during BP therapy, have the potential to reduce the risk of ONJ. Furthermore, myeloma patients who develop ONJ after dental procedures are less likely to have recurrence or nonhealing lesions after BP reinitiation following ONJ healing compared with those who develop spontaneous ONJ lesions. As BPs remain the cornerstone for the management of myeloma bone disease, it is important to identify patients at a higher risk for development of ONJ.

Genetic variants are associated with disease susceptibility. The recently developed single nucleotide polymorphism (SNP) array enables simultaneous detection of a large number of DNA polymorphic loci in a simple way. Using this technology Sarasquete et al evaluated half a million SNPs in 2 groups of myeloma patients who received the same induction therapy. The first group included 22 patients who developed ONJ and the second included 65 patients who...
CYP2C8 are associated with side effects of the malarial drug amodiaquine, and the hypoglycemia of the anticancer drug paclitaxel, the alterations for this finding is that CYP2C8 is also involved in the metabolism of about 20% of clinically used drugs. All members of the CYP2C gene subfamily, namely CYP2C8, CYP2C9, CYP2C18, and CYP2C19, are polymorphic. CYP2C8 plays a significant role in the metabolism of the anticancer drug paclitaxel, the anti-malarial drug amodiaquine, and the hypoglycemic agent troglitazone, as well as amiodarone, verapamil, and ibuprofen. Polymorphisms of CYP2C8 are associated with side effects of the aforementioned drugs. The CYP2C8*3 and CYP2C9*2 are the major variant alleles in whites. However, it is difficult to find a biological link between the rs1934951 polymorphism of the CYP2C8 and the development of ONJ in myeloma patients who receive BPs, as CYP2C8 is not involved in the metabolism of BPs and the rs1934951 polymorphism is placed in an intronic region, which theoretically should not imply alterations at the protein level. Possible explanations for this finding is that CYP2C8 is also involved in the initiation of the 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMG-CoAR) pathway, a biological key metabolic cascade for cholesterol synthesis, which can be inhibited by BPs, and also that CYP2C8 metabolizes arachidonic acid to epoxyeicosatrienoic acids, which play a key role in the regulation of vascular tone and cardiovascular homeostasis. However, these hypotheses have yet to be proven.

The value of the study by Sarasquete et al is that, for the first time, a genetic variable is associated with the development of ONJ. The confirmation of these results may lead to the recognition of a subset of myeloma patients who are predisposed to develop ONJ after intravenous BPs. For these patients, a different approach for bone maintenance or BP administration may need to be considered.

Conflict-of-interest disclosure: The authors have received honoraria for participating on Novartis advisory boards.

REFERENCES

TAFI: structured for self-destruction

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The elusive mystery surrounding the intrinsic thermal instability of TAFI has finally been solved, thanks to the determination of the first crystal structure of TAFI, which uncovers a highly dynamic local structure responsible for its self-destruction.

An important regulator in the blood coagulation system, linking the systems of coagulation and fibrinolysis,1,2 thrombin-activatable fibrinolysis inhibitor (TAFI) plays a significant physiological role, a role strictly controlled by a unique and mysterious autoregulatory mechanism. Since its discovery in the mid-1990s, a tremendous amount of effort has been invested in TAFI research, with more than 400 papers published in just 14 years (reviewed in Boffa and Koschinsky,3 Nesheim and Bajzar,4 and Bouma and Mosnier5).

Similar to many other procarboxypeptidases, the TAFI zymogen is activated through cleavage of an activation peptide to form activated TAFI (TAFIa), which is involved in the inhibition of plasmin-mediated clot lysis. However, once activated, TAFIa “destroys” itself in a matter of minutes, an act beautifully synchronized with the physiological process. Indeed, it has been long known that this “suicidal” action is achieved by the intrinsic structural instability of TAFIa.6,7 However, the molecular mechanism and structural basis underlying this “time bomb,” which leads to its self-destruction, have remained elusive. The striking difference in stability between TAFIa and other carboxypeptidases, despite high sequence homology (over 40% identity with human procarboxypeptidase B, for example), has left researchers completely puzzled until now.

The determination of the X-ray structure of TAFI by Marx and colleagues represents a major breakthrough in solving this mystery. At first glance, the overall structure, which is quite similar to those of other carboxypeptidases, provides no surprises or immediate clues to the underlying basis for TAFI’s intriguing dynamic instability. Indeed, this would explain why molecular modeling has not been informative.8 However, the “devil” is in the details. Through careful and systematic structural analyses, Marx et al have discovered a flexible “flap” that controls the fate of TAFI. The temperature factors (an indicator of thermal flexibility) in the “flap” segment are significantly higher than the average for the whole protein for each of the 3 crystallographically-independent molecules. This fact is further supported by the varying electron density levels for this region among the 3 molecules. These results, in conjunction with inhibitor complex and mutant structures, convincingly demonstrate that this “flap” is the “time
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