Introduction

The purpose of this chapter is to examine the role of platelet-derived growth factor (PDGF) in the vascular smooth muscle (VSMC) hyperplastic response that occurs in the intima of arteries after balloon angioplasty. This proliferative response results in the reappearance of stenoses in approximately 40% of the patients undergoing coronary balloon angioplasty. To place into perspective the role of PDGF in restenosis, the evidence implicating VSMC proliferation as the cause of restenosis and the approaches that have been used but have failed to resolve the problem are presented. Thereafter, recent cell and molecular biology studies which provide a foundation for the understanding of sources and possible roles of PDGF in restenosis are presented. Finally, PDGF release after angioplasty is described.

Balloon angioplasty

The concept of angioplasty was first introduced by Dotter and Judkins [1] who demonstrated that the lumen of an artery could be enlarged by introducing into the lumen successively larger coaxial catheters. However, angioplasty did not become popular until after the introduction of the balloon angioplasty technique by Gruentzig in 1978 [2]. In balloon angioplasty, a balloon-tipped catheter is positioned in an artery at the site of a hemodynamically significant stenosis. The artery is then irreversibly stretched and the lumen enlarged by inflating the balloon.
Restenosis

After several years of experience with angioplasty, it became apparent that one of the most severe long-term side effects of angioplasty was the reappearance of the stenosis several months after the dilatation, a phenomenon referred to as restenosis [3]. Restenosis occurs often and quickly. For example, in a recent study, Nobuyoshi et al [4] performed repeated coronary angiography on 229 patients that had undergone coronary angioplasty. They found that 1, 3, 6, and 12 months after angioplasty the restenosis rates were 13%, 43%, 49%, and 53%, respectively.

Histologic studies of necropsy specimens [5] and specimens of restenotic lesions obtained by atherectomy [6] have both implicated intimal VSMC hyperplasia and extracellular matrix deposition as primary causes of restenosis in man. VSMC hyperplasia after angioplasty has also be observed in other species including rabbits [7] and pigs [8]. However, restenosis need not always be the result of VSMC hyperplasia. Waller et al [9], in their study of restenotic human coronary arteries obtained 1 -24 months after successful dilatation, found that 40% of the arteries had no evidence of a previous angioplasty and inferred that restenosis, in these cases, was the result of arterial elastic recoil.

Prevention of restenosis

Pharmacologic interventions

Once the pathologic changes produced by angioplasty were understood and restenosis had been identified as a clinical problem, PDGF was presumed to be involved. Facts implicating PDGF included the finding of platelets adherent to the luminal surfaces of balloon-dilated arteries shortly after angioplasty [8,10] and prior knowledge that PDGF is one of the factors released from alpha-granules upon platelet adhesion, that PDGF is a potent chemoattractant and mitogen for VSMCs, and that PDGF had been implicated as a factor involved in the genesis of atherosclerosis (the response-to-injury hypothesis) [11]. Based upon the presumption that platelet deposition and PDGF release were intimately involved in restenosis, several clinical studies were performed using drugs with antiplatelet properties. Unfortunately, no studies to date have demonstrated any inhibition of restenosis by antiplatelet agents. [3,12] However, Chesebro et al [13] did report that aspirin and dipyridamole reduced acute complications after angioplasty from 20% to