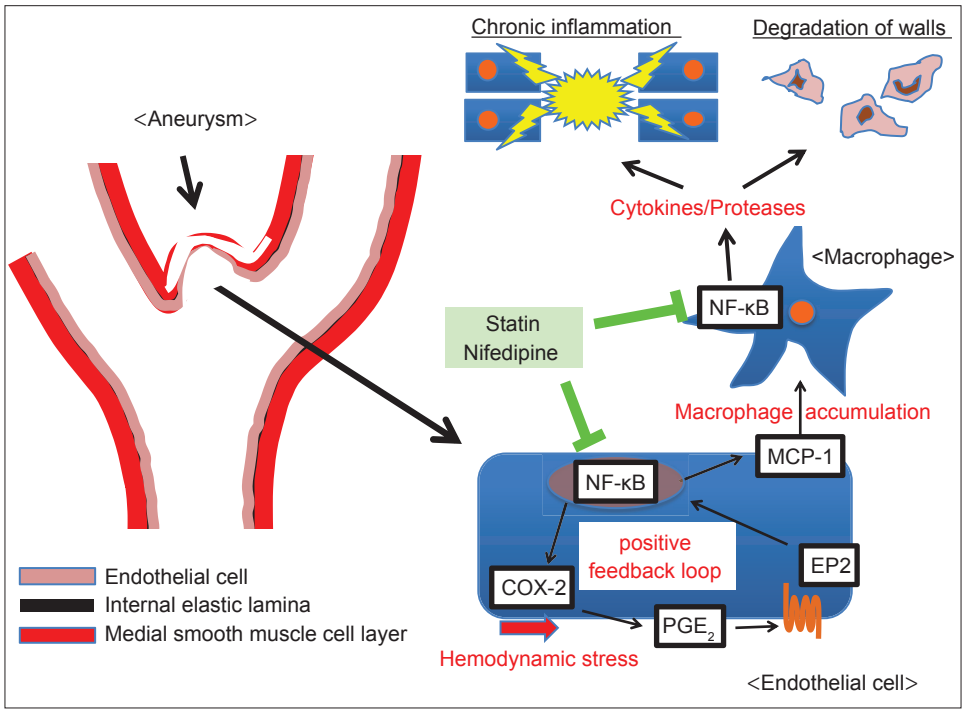

Figure 1: Schematic drawing of the mechanisms that regulate aneurysmal formation and progression. PGE_2: prostaglandin E_2; COX-2: cyclooxygenase-2; MCP-1: monocyte chemoattractant protein-1; NF-κB: nuclear factor-kappa B

tissue degeneration observed in CAs[31,35] [Figure 1]. The critical contribution of MCP-1 mediated macrophages recruitment/infiltration in the pathogenesis is clearly shown by recent experimental reports in which the deficiency of MCP-1, administration of the dominant negative form of MCP-1 (7-ND), or depletion of macrophages by clodronate liposome all significantly suppressed CA formation and progression.[31,35]

The remaining question to be solved is whether the processes are regulating the initiation and progression of CAs are different. This important issue remains to be elucidated. As an initiation, as well as the progression of CAs, can be suppressed by inhibiting the inflammatory processes in lesions, these two steps of the pathogenesis presumably share the same underlying mechanisms in terms of inflammation. However, because the hemodynamic status surrounding CA lesions is completely different (e.g. a high hemodynamic status at the prospective site of the initiation[46,47] but a low hemodynamic status in the dome of the enlarging CAs[48,49]), there must be some differences in the processes that regulate the initiation and progression of CAs, and this is worthy of investigation.

In summary, based on the recent studies on CAs, long-lasting inflammatory responses in arterial walls play a crucial role in CA formation and progression, and NF-κB mediates this inflammation as a major transcription factor that regulates inflammation. In addition, the presence of a vicious cycle/positive feedback loop (i.e. NF-κB activation and macrophage infiltration via the NF-κB-induced MCP-1 expression) seems to be two major mechanisms that contribute to the amplification, expansion, and chronicity of inflammatory responses.

This recent experimental evidence on the role of inflammation in CAs may be useful in developing of therapeutic drugs for CA treatment. Recent experimental studies in human and rodent models have greatly advanced our understanding of the pathogenesis of CAs, making it more likely that the current treatment of CAs will be improved.

POTENTIAL OF ANTIINFLAMMATORY DRUGS FOR TREATING CEREBRAL ANEURYSMS IN ANIMAL MODELS

As discussed, a long-lasting inflammatory response is detected in CA lesions, which plays a crucial role in the pathogenesis of CAs. Recent findings in rodent models have amassed evidence indicating the therapeutic effect of antiinflammatory drugs on the further enlargement or rupture of CAs and have proposed the potential of these drugs for treating CA.[31,33-36,50-58] Among these drugs that have a suppressive effect on CAs in animal models, statin,[50,51,55] nifedipine,[52] and emedastine difumarate[53] are already used in humans with clinical indications. Therefore, these drugs are good candidates for treating CAs in humans to prevent rupture or enlargement. We summarize the effect of these drugs on CAs in animal models.

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