Epilepsy is a neurological disorder affecting approximately 1% of the worldwide population. Despite the availability of antiepileptic drugs, one-third of patients are considered “drug-resistant” and fail to achieve seizure control. In the last decade, many breakthroughs have been made in identifying different mutated genes linked to severe epilepsy, which have brought new molecular players as potential therapeutic targets. Moreover, a link between epilepsy and inflammation, which has now become an important component of the disorder, has brought several inflammatory-linked mediators as further potential therapeutic targets. To this regard, a critical role has also been suggested for blood vessels, as an altered vascularization or an abnormal response of the vessel wall during the seizure may participate to the progression of damage in the epileptic tissue. Finally, all these players could significantly modulate the process of epileptogenesis, for which regulatory pathway such as that depending on the mammalian target of rapamycin (mTOR) are intensively studied to dissect the mechanisms leading to the development of an epileptogenic environment.