Structure comparison of human glioma pathogenesis-related protein GliPR and the plant pathogenesis-related protein P14a indicates a functional link between the human immune system and a plant defense system

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ABSTRACT The human glioma pathogenesis-related protein (GliPR) is highly expressed in the brain tumor glioblastoma multiforme and exhibits 35% amino acid sequence identity with the tomato pathogenesis-related (PR) protein P14a, which has an important role for the plant defense system. A molecular model of GliPR was computed with the distance geometry program DIANA on the basis of a P14a–GliPR sequence alignment and a set of 1,200 experimental NMR conformational constraints collected with P14a. The GliPR structure is represented by a group of 20 conformers with small residual DIANA target function values, low AMBER energies after restrained energy-minimization with the program OPAL, and an average rms deviation relative to the mean of 1.6 Å for the backbone heavy atoms. Comparison of the GliPR model with the P14a structure lead to the identification of a common partially solvent-exposed spatial cluster of four amino acid residues, His-69, Glu-88, Glu-110, and His-127 in the GliPR numeration. This cluster is conserved in all known plant PR proteins of class 1, indicating a common putative active site for GliPR and PR-1 proteins and thus a functional link between the human immune system and a plant defense system.

The glioma pathogenesis-related protein (GliPR) is highly expressed in the tumor glioblastoma multiforme (1), which arises from brain immune cells and accounts for over 65% of all human primary brain tumors (2). GliPR was found in all glioma cell lines and tumors studied, but was not detectable in any normal fetal or adult tissues, including normal brain, suggesting that GliPR plays an important role for tumor growth. High levels of GliPR expression can also be induced with phorbol ester in macrophages (1), which are active at the front line of the human immune system. RTVP-1, another protein that was recently found in glioblastoma multiforme (3), is almost identical to GliPR. Compared with GliPR, RTVP-1 possesses both an additional N-terminal signal sequence and a C-terminal putative transmembrane segment. Although RTVP-1 was found to be expressed also in various normal tissues, it cannot be excluded that its high expression in the tumor cells is also related to their malignant properties. GliPR and RTVP-1 exhibit high sequence homology with the plant pathogenesis-related proteins of group 1 (PR-1 proteins), which play a central role for the defense system of plants (4), for example, during the manifestation of systemic acquired resistance (5). Because proteins with a sequence identity larger than 30% are commonly believed to adopt the same fold (6), this homology is suggestive of a structural link between the human immune system and the defense system of plants (1).

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Abbreviations: PR, pathogenesis-related; GliPR, glioma PR protein; PAM, accepted point mutation; RTVP-1, related to testes-specific, vespid, and pathogenesis proteins; PIR, Protein Identification Resource.