Cancer Biology

ASPP are a new family of tumour suppressor genes which connects polarity and growth

Recent studies looking at mutations in ASPP proteins have shown cell polarity is severely affected, in both developing and mature tissue. This morphological change could be a factor which determines how tumours progress.

A disproportionately large number of human cancers are found in epithelial tissue. Epithelia are one cell layer thick and characterised by tight junctions between cells. A distinct change in morphology can be seen between the apical and basal surfaces of each cell. New research into the ASPP family of proteins has shown they are a required component of tight junction formation, and loss of their function will cause a great reduction in cell polarity.

Ankeryin repeat, Sh3, proline rich domain proteins (ASPP) are so named due to their conserved C-termini region[1]. They are a well characterised binding partner of the tumour suppressor p53, but unlike most proteins, ASPP binds to the DNA-binding region of p53. This property enables a direct influence over what DNA sequences p53 can interact with. The most well characterised p53 pathways are the cellular senescence pathway, and the cell death pathway. The ASPP proteins seem to directly potentiate a cell death, or apoptosis, fate without altering senescence. This occurs through selectively increasing binding of p53 to Bax gene promoter regions. It is here that the three family members diverge in function; ASPP1 and ASPP2 promote apoptosis, whilst the third member, iASPP, has the opposite effect.

Over 25,000 mutations have now been identified which affect the p53 pathway[2], however less work has been done on quantifying what physical effect each mutation has on a cell, and how this pushes it towards a tumour fate. Professor Xin Lu from the Ludwig institute for cancer research based at Oxford University was the first to identify the ASPP family, and her group has continued to be at the

forefront of research in the area[3]. Due to the high priority given to cancer research, little work has been done to discover what function ASPP holds within a normal cell. The large proportion of ASPP-mediated cancers being found to involve epithelial tissue has allowed a more detailed study of what ASPPs do.

Visualisation of ASPP within epithelial cells showed it situated near the apical cell surface, and also found co-localised with the Polarity complex protein, PAR3. Polarity complex proteins are an essential component of tight junctions within epithelia. It is the tight junction which forms an impermeable barrier between cells which in turn enables the high degree of basal and apical polarity. In drosophila, polarity complex proteins have been shown to have tumour suppressor role; a term indicating that mutations could lead to the onset of a cancerous cell fate. To determine what role ASPP were having at the cell surface, an ASPP2 knock out mouse model was made; this caused the PAR3 complex to lose its close association with the apical cell surface and, as a result, tight junctions were decreased by 70%. This loss had the expected detrimental effect on cell polarity, which in turn would severely affect the function of the epithelial tissue. The normal role of ASPP in tight junction formation has not been discovered, but the fact it is needed for formation suggests it may hold a scaffold role; perhaps recruiting proteins into a tight junction complex. Further study will be required to determine the order of events which lead to junction formation.

The mouse knockout of ASPP2 has allowed conjecture on the process which leads to p53 initiation. During a naturally occurring mutation in the tight junction complex, ASPP may be prevented from binding to its normal partners, and this could lead to its translocation to the nucleus and binding with p53. Conversely, if ASPP is mutated, a number of its natural functions could be removed. Inability to bind PAR proteins may cause loss of epithelial polarity; mutations in other proteins may not be recognised by ASPP, or ASPP binding to p53 may be less efficient. Another factor could be mutations in p53 itself. The DNA binding domain is responsible for 80% of mutations in p53, thus changes in this area could prevent ASPP binding, and stop the apoptosis pathway being initiated.

The discovery of ASPP proteins was relatively recent and these new studies which have linked ASPP mutation with epithelial cell polarity have created many more questions than they have answered. A great deal of work, both using tissue culture and mouse models will be required to elucidate the intricate detail of the ASPP-p53 pathway.

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Bibliography

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