

## PAPER 20

### Expression of Angiogenesis Markers HSP70, HSP90, VEGF and pERK1/2 in Both Components of Dedifferentiated Chondrosarcomas

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**Background:** Dedifferentiated chondrosarcomas (DDCS) are highly aggressive bimorphic mesenchymal neoplasms with poor outcomes and limited treatment options. Genes and proteins involved in angiogenesis play essential roles in the development of invasion and metastasis. Several factors influence this process including vascular endothelial growth factor (VEGF) and heat-shock proteins (HSPs). In an effort to elucidate the roles of these factors, a cohort of DDCS was evaluated for immunohistochemical expression of VEGF, extracellular signal-related kinase (ERK) 1/2, and HSP70. A paired set of 8 DDCS cases was interrogated by RNA sequencing for differences in gene expression of angiogenesis markers in the two tumor components.

**Methods:** 376 chondrosarcomas were identified from 1997 to 2018 in the Department of Pathology files. A subset of 29 DDCS was derived and tissue microarrays were constructed to include both well-differentiated and dedifferentiated components. Antibodies against HSP70, ERK1/2 and VEGF were applied with appropriate controls using standard methods. Expression was tabulated as nuclear and/or cytoplasmic, intensity (0, 1+, 2+, 3+) and diffuse/ focal staining. Results were analyzed by the student t-test. RNA sequencing of a paired set of 8 DDCS cases employed the Nextseq500 platform and SMART technology. Data were analyzed using Edge R 4.0, Fisher's exact test and principal component analysis.

**Results:** There were 11 females and 18 males and the most frequent site of involvement was the extremity. VEGF immunohistochemical expression was present in both well differentiated and dedifferentiated components. Higher immunohistochemical expression of HSP70 and pERK1/2 were noted in the dedifferentiated component, respectively,  $p=0.003$  and  $p=0.02$ . RNA sequencing showed higher expression of several *HSP* family members, including *HSP70* and *HSP90* in the dedifferentiated component. Furthermore, high mobility group AT-hook 2 (*HMAG2*) and *SET* nuclear proto-oncogene demonstrated higher expression in the dedifferentiated component,  $p<0.05$ .

**Conclusions:** The well-differentiated and dedifferentiated components of DDCS are different, histologically and transcriptomically. The dedifferentiated component of DDCS shows higher expression of markers associated with malignant behavior. Some of these may represent future treatment targets against the metastatic potential of these aggressive tumors.