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Cancer Science & Pediatrics 2019: Insight into Sarcoma Biology from Sarcoma Cell Line Progression Series - Jiri Hatina - Charles University Medical Faculty in Pilsen, Czech Republic

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Soft tissue sarcomas are known for their great variability in clinical behavior, ranging from almost indolent lesions to rapidly metastasing tumours. Genes responsible for sarcoma progression have been poorly characterized by now. Towards this end, we comprehensively analyzed transcriptomes of two single-background progression series of murine sarcoma cell lines. The first one, established by us from consecutive fibrosarcomas in a v-jun transgenic mouse, consisted of the slowly proliferating nonmotile and noninvasive cell line JUN-2, rapidly proliferating, motile and invasive cell line JUN-3, and the cell line JUN-2fos-3 that exhibits a unique transformation pattern, with little deregulation of cell growth and proliferation, but pronounced motility and invasiveness.

The second one, established by a french group, consisted of the widely used pre-adipocytic cell line 3T3L1 and its derivative liposarcoma cell line LM3D. From both liposarcoma cell lines, we isolated putative liposarcoma stem cells (as side-population cells).

We performed four sets of genome-wide transcriptomic analyses. The JUN-fibrosarcoma progression series, by virtue of its unique distribution of transformation related-traits between individual cell lines, made us possible to identify two separate groups of genes tentatively involved in sarcoma progression in a single transcriptomic analysis on the one hand, proliferation-related genes could be identified by their differential expression in JUN-3 compared to both JUN-2 and JUN-2fos3, and, on the other hand, motility and invasiveness-related genes could be identified by their common expression pattern in JUN-2fos3 and JUN-3 cells compared to JUN-2.

With regard to the liposarcoma progression series, we identified, on one hand, progression genes, by their differential expression in pre-adipocytic 3T3L1 cells versus liposarcoma LM3D cells, and, on the other hand, stemness genes, by profilling side-population cells versus non-side population cells from both cell lines.

The high-throughput gene expression analysis has been performed using the GeneChip mouse genome 430 2.0 array (ThermoFisher Scientific). Finally, we identified a small group of genes co-regulated in both JUN-3 and LM3D highly transformed cells ("sarcoma progression" signature). A striking feature of this "sarcoma progression" signature is the complex downregulation of the canonical Wnt/β-catenin signalling pathway. Upregulated genes involve an extensive array of genes with published function as Wnt/β-catenin inhibitors (Dickkopf-2 and -3, Apcdd1, Meg3, Fibulin-5, Ints6, Msx1), on the other hand, the expression profile strongly suggest activation of the Wnt5-Ror2 noncanonical pathway. Another extensive gene set includes genes, whose elevated expression portends poor prognosis in various carcinomas, whose expression in sarcomas have not been analyzed by now, nevetheless.

These genes include Snx6, uea transporter Slc14A1, Dpysl3, Ulk2, transient receptor potential calcium channel Trpc1, Steap3, Morc4, Crp2 and Coronin 1C). Some of the genes have already been described as poor prognostic indicators in certain soft tissue sarcoma types or in osteosarcoma (Tbx3, Tgfbi, Rab3ip, Alcam, Crabp1, Ecm1, periostin).

Interestingly, although the bulk cell population of both the fibrosarcoma and liposarcoma progression series provided the input into the analysis, a part of the upregulated genes in the "sarcoma progression" signature is strongly reminiscent of stemness activation (c-jun and genes coding for its activators– Ddx21and Mfap, as well as genes coding for stemness associated alternative splicing factors Khdrbs3 and Mbln3, as well as Lis1, which seems to be involved in assymetric stem cell division).

Otherwise, stemness regulation seems to be dominated by distinct factors in both respective sarcoma progression series, with Sox-2 being a probable candidate in JUN-3 fibrosarcoma cells, and extensive array of Hippo-pathway genes (Yap, FoxM1, Pttg, Tacc3, Btf3, as well as Lats2) being upregulated in both the adipocytic and liposarcoma stem cells. We believe that our models and differentially expressed genes identified by their transcriptomic analysis can provide important new information on biology of soft tissue sarcoma and may help to identify new prognostic markers and potential therapeutic targets for this rare and highly heterogenous tumour type.

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